FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

Date: May 24, 2012

Time: 8:30 AM - 4:30 PM

Location: Food and Drug Administration
White Oak Campus
Building 31, The Great Room
Silver Spring, Maryland

MEETING ROSTER

DESIGNATED FEDERAL OFFICER (Non-Voting)
Glendolynn S. Johnson, Pharm.D., Division of Advisory Commitee & Consultant Management, Office of Executive Programs, CDER, FDA

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBERS (Voting)
Jeffrey A. Cohen, M.D., Professor, Neurology, Dartmouth Medical School, Section Chief, Neurology, Director, Clinical Neurophysiology Fellowship, Dartmouth Hitchcock Medical Center
Nathan B. Fountain, M.D. (Acting Chairperson), Professor, Department of Neurology, Director, FE Dreifuss Comprehensive Epilepsy Program, University of Virginia School of Medicine
Samuel A. Frank, M.D. (Consumer Representative), Associate Professor of Neurology, Boston University School of Medicine
Ellen J. Marder, M.D., Staff Physician, Dallas Veterans Affairs (VA) Medical Center, Clinical Associate Professor of Neurology, University of Texas Southwestern Medical School

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)
Lynn Kramer, M.D., FAAN (Industry Representative), President, Neuroscience PCU, Eisai, Inc.

TEMPORARY MEMBERS (Voting)
Emilia Bagiella, Ph.D., Professor of Biostatistics, Department of Health Evidence and Policy, Mount Sinai School of Medicine
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Robert R. Clancy, M.D., Professor of Neurology and Pediatrics, The University of Pennsylvania School of Medicine, The Children's Hospital of Philadelphia
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MEETING ROSTER (CONT'D)

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Russell G. Katz, M.D., Director of Neurology Products (DNP), ODE-I, OND, CDER, FDA

MEETING ROSER (CONT'D)

Ronald Farkas, M.D., Ph.D., Clinical Team Leader, DNP, ODE-I, OND, CDER, FDA
Devanand Jillapalli, M.D., Medical Officer, DNP, ODE-I, OND, CDER, FDA
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AGENDA

P R O C E E D I N G S

DR. JOHNSON: Good morning. I would like to first remind you all to please silence your cell phones, your BlackBerrys, and other devices if you have not done so already.

I would like to identify the FDA press secretary, Sandy Walsh. Please stand if you're in the room.

DR. FOUNTAIN: Good morning. Welcome to the advisory committee meeting. Before we begin, why don't we go around the table and have introduction of the committee members and consultants? And why don't we start at this end?

DR. UNGER: I'm Ellis Unger. I'm acting director of the Office of Drug Evaluation I, FDA.

DR. KATZ: Russ Katz, director of the Division of Neurology Products, FDA.

DR. FARKAS: Ron Farkas, the clinical team leader in the Division of Neurology Products, FDA.

DR. JILLAPALLI: Devanand Jillapalli, medical officer, Division of Neurology Products, FDA.

DR. LUAN: Julia Luan, statistician.

DR. ENSRUD: Erik Ensrud from the Boston VA Medical Center in Brigham Women's Hospital.

DR. ROSENBERG: Paul Rosenberg from Johns Hopkins University.

DR. GOOCH: Clifton Gooch, the University of South Florida.

DR. LOGIGIAN: Eric Logigian, University of Rochester Medical Center.

DR. MIELKE: Michelle Mielke, Mayo Clinic.

DR. CLANCY: Robert Clancy, Children's Hospital, Philadelphia, University of Pennsylvania.

DR. FOUNTAIN: Nathan Fountain, University of Virginia.

DR. JOHNSON: Glendolynn Johnson, DFO, PCNS.

DR. FRANK: Sam Frank, Boston University, and I am the consumer representative.

MS. HOUSE: Tiffany House, patient representative.

DR. MARDER: Ellen Marder, neurologist, UT Southwestern and VA Medical Center.

DR. BAGIELLA: Emilia Bagiella, Mount Sinai School of Medicine.

DR. OAKLANDER: I am Anne Louise Oaklander from the Department of Neurology at Massachusetts General Hospital.

DR. VERMA: Ashok Verma, University of Miami.

DR. PRESTON: David Preston, Case Western Reserve University, Cleveland, Ohio.

DR. SHEFNER: Jeremy Shefner, Upstate Medical University in Syracuse, New York.

DR. COHEN: Jeffery Cohen, Dartmouth Medical School.

DR. KRAMER: Lynn Kramer, industry representative.

DR. FOUNTAIN: Thank you. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held.

Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a

productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or during lunch. Thank you.

Now, I'll pass it to Lieutenant Commander Glendolynn Johnson, who will read the conflict of interest statement.

DR. JOHNSON: The Food and Drug Administration is convening today's meeting of the Peripheral and Central Nervous System Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary

members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C., Section 208 and Section 712 of the Food, Drug, and Cosmetic Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have a potential financial conflict, when it is determined that the agency's need for a particular individual's services outweigh his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress

has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and temporary members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimonies, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

At today's meeting, the committee will discuss the safety and efficacy of new drug application 202737, proposed trade name, Vyndaqel, tafamidis capsules, submitted by FoldRX Pharmaceuticals, a subsidiary of Pfizer. The proposed indication is for the treatment of transthyretin familial amyloid polyneuropathy.

This is a particular matters meeting, during

which specific matters related to FoldRX and Pfizer's Vyndaqel will be discussed. Based on the agenda and all financial interests reported by the committee members and temporary members, no conflict of interest waivers have been issued in connection with this session. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Lynn Kramer is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Kramer's role in this meeting is to represent industry in general and not any particular company. Dr. Kramer is employed with Eisai.

Dr. Kramer would like to disclose that Eisai and Pfizer currently have a co-promotion agreement for Aricept, an unrelated product.

We would like to remind members and temporary members that, if the discussion involve any other products or firms not already on the agenda for which

an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships they may have with the firm at issue. Thank you.

DR. FOUNTAIN: All right. We'll now proceed with Dr. Katz's introductory remarks.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting. Likewise, FDA encourages you, at the

beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking, though.

Dr. Katz?

DR. KATZ: Thank you, Dr. Fountain.

First, let me welcome the committee members, the already-appointed standing committee members. We have a number of members who I guess are awaiting final sign-off to be official committee members, but I appreciate very much your agreeing to be members and for coming this morning. I also would like to thank our patient representative.

I'd also like to thank the folks who signed up to speak in the open public hearing. Your comments are very important to the process, and I appreciate very much your making the effort to come today.

So as you know and as we've heard, of course, we're here to discuss NDA 202737, submitted by Pfizer, Incorporated for the use of tafamidis meglumine,

proposed name Vyndaqel, in the treatment of patients with familial amyloid polyneuropathy, which I'll refer to as FAP.

FAP is caused by one of numerous mutations in the gene that codes with transthyretin or TTR. TTR occurs normally as a tetramer, and it's a transporter of thyroxin and the retinal binding protein retinal complex. In a normal case, it exists as a tetrameric in equilibrium with its component monomers. In patients with FAP, though, the mutation causes the tetramer to dissociate into abnormal monomers that misfold, form toxic intermediates, ultimately resulting in the formation of amyloid, which deposits in numerous tissues.

There are numerous phenotypes. In FAP, the primary, though certainly not the sole, organ of injury is the peripheral nerve. Patients with FAP develop signs of a severe progressive sensory motor and autonomic neuropathy. Symptoms can begin in the third, fourth, or fifth decade and death usually ensues, on average, within 10 or so years after the onset of symptoms.

Other mutations can result in other primary organs of toxicity, especially the heart, resulting in a condition called familial amyloid cardiomyopathy or FAC. The most common mutation causing FAP results in a substitution of valine by methionine at position 30, and this is the so-called V30M mutation.

There are no specific current treatments for FAP, other than liver transplant. Because the abnormal tetramer is produced in the liver, a liver transplant is helpful. Of course, not everyone can get a liver transplant.

This is an orphan disease, meaning, by law, it has a prevalence of less than 200,000 patients in the United States. And in fact, the prevalence of FAP in the U.S. is somewhere around 2500, maybe less, and the worldwide prevalence is somewhere between 5,000 and 10,000, presumably. And patients are clustered geographically, and there are larger clusters in Portugal, Sweden, and Japan.

Tafamidis, which is the drug under discussion today, binds to the two thyroxin binding sites of the tetramer and presumably stabilizes the tetramer, so

presumably fewer toxic monomers are produced, hence, less amyloid is formed and deposited in tissues. And the sponsor asserts that it is this action of tafamidis that can slow the progression of the disease.

In support of this claim, the sponsor has submitted the results of a single, adequate, and well-controlled study, so-called Study 005, which was performed in patients only with the V30M mutation.

In addition, the sponsors performed Study 006, which is a follow-on open-label study to 005 in which patients who had received placebo in 005 were switched to treatment with tafamidis, and patients who had been randomized to tafamidis in 005 continued to receive tafamidis for another 12 months.

Although Study 006 was open label, the patients and investigators were blinded to their original treatment in Study 005. And in addition, the sponsors performed several other and submitted the results of several other open-label, uncontrolled studies, which enrolled patients both with the V30 mutation and with other mutations.

So my goal here this morning in my brief

remarks is twofold. One, I want to just give an overview of the issues that we are concerned about in the data that was submitted. Dr. Farkas will present later this morning a much more detailed presentation of the issues that we are concerned about and why we're concerned about them, but I just want to touch on them briefly. But the other purpose of my remarks is to give you a background into the relevant regulatory pathways to potential approval for any drug, really. I think it's important for the committee and other folks to understand what regulatory pathways are available for drug approval. So let me start with that.

The sine qua non for drug approval in the United States is a demonstration of what's known as substantial evidence of effectiveness. And since 1962, the law has required this sort of evidence to be provided before a drug can be approved for marketing.

Substantial evidence of effectiveness was defined in the law -- it's still defined -- as evidence from what are called adequate and well-controlled clinical investigations that establish that the drug has the effect claimed for it in product labeling. And

it's important to note that the language of the law is in clinical investigations, plural. And typically, in practice and traditionally, this standard has been considered to have been met if at least two adequately designed and conducted clinical trials demonstrate statistically significant between-treatment contrasts on prospectively defined, clinically relevant outcome measures. And this incorporates the standard scientific requirement for independent replication of any finding.

Traditionally, statistical significance has been defined as a two-tailed p value of less than 5 percent for the between-treatment contrast. That's a definition you all know of statistical significance that is deeply embedded in the culture of clinical trials and drug approval. It's the standard from which we rarely waver. And when we do, we do so with some trepidation.

In 1997, the law was amended to include an additional definition of substantial evidence of effectiveness. The new definition stated that substantial evidence can consist of the results of a

single, adequate and well-controlled trial with something called confirmatory evidence.

The law didn't specify under what circumstances this new standard might apply, nor did it define what it meant by confirmatory evidence. Nonetheless, the agency, in 1998, issued a guidance document that described the aspects of a single study that might make it meet the new single-study standard. Among these characteristics -- these are not all of them -- but among the characteristics are a very low p value, a p value considerably lower than the standard two-tailed .05, on the primary outcome or outcomes; multiple secondary outcomes reaching a dependent statistical significance, or very nearly so, especially on outcomes that were not just highly correlated with each other, but which assessed significantly different clinical domains; multiple subgroups of patients all showing similar effects, in other words, mildly impaired patients, severely impaired patients, that sort of thing; multiple study sites showing effects; and no one particular study site providing all the persuasive evidence.

So in other words, this one study would presumably provide the sort of, I guess you could say, internal replication that two studies would provide under the usual standard. And it would be considered to provide, in a sense, the same amount of evidence of effectiveness as two typical studies.

Depending upon the robustness of the single study, the confirmatory evidence required by the law could be provided by that single study itself or confirmatory evidence could come from a source external to that study. It's also worth noting that the standard still that is most commonly applied is the two-study standard.

I need to discuss another relevant regulatory pathway before we move on. Since 1992, the agency has had the authority to approve a treatment on the basis of an effect on what I would call an unvalidated surrogate marker. This approach you probably have heard of as accelerated approval or subpart H approval, subpart H being the section in the regulations that describes this approach.

So briefly, you undoubtedly all know a

surrogate marker is typically a lab test that has no immediate direct bearing on how the patient feels or functions, something like blood pressure or an imaging marker, but that serves as the primary measure of drug effect for purposes of drug approval. And less commonly, actually, a clinical outcome can serve as a surrogate if it's not the clinical outcome ultimately that you really care about, but an effect on which might predict the ultimate clinical outcome. An ultimate clinical outcome of interest might be something like mortality.

The agency, of course, has long approved drugs based on their effects on surrogates when data has established that an effect on that surrogate, a drug-induced effect on that surrogate, is known to produce -- there's evidence that it will produce, usually out in time -- an effect on the clinical outcome of interest. So blood pressure drugs are approved on the effect of some blood pressure because it's known that that predicts fewer strokes, fewer heart attacks in the future.

These surrogates are called validated

surrogates because we know, based on evidence, that when you affect a surrogate, you will affect the clinical outcome of interest down the road. But in contrast to validated surrogates, there are surrogates for which drug-induced effects are predicted to result in a beneficial clinical effect, but we don't really know yet that they do predict that clinical benefit. And these are what I would call unvalidated surrogates. And again, the agency has the authority to approve a drug based on its effects on such a surrogate if we find that the effect on the surrogate is reasonably likely to predict the clinical benefit we care about. And that's language of the law, reasonably likely to predict a clinical benefit.

It's very important, I think, to understand that concluding that an effect on an unvalidated surrogate will be reasonably likely to predict a clinical benefit will typically depend upon a detailed understanding of the effects, both positive and negative, of the drug under study as well as a detailed understanding of the path of biological pathways of the disease that lead to clinical symptoms. This is

information that we typically don't have. We typically don't know all the effects, good and bad, of a drug. And we certainly typically don't know all the pathophysiology pathways that lead to disease in any given case.

Although there is often a clear correlation between a proposed surrogate and disease progression in the untreated state, it may very well be the case that under treatment conditions, this relationship no longer exists.

There are numerous examples in medicine in which an expected beneficial effect on the proposed surrogate did not translate into a clinical benefit. And because approval based on an effect on an unvalidated surrogate, accelerated approval, subpart H approval, involves considerable uncertainty about the clinical benefit to be obtained, the regulations require that sponsors perform studies in the post-marketing period to actually document that the drug in fact does have the effect of the clinical benefit predicted. And if these studies aren't done in a timely manner or if the studies are done and they

actually show that there is no clinical benefit, these drugs can be removed expeditiously from the market.

At this point, I have to make something clear to bring together these sorts of regulatory approaches, and it's something that I think is commonly misunderstood. In order for us to approve a drug on the basis of an effect on such an unvalidated surrogate -- again, accelerated approval -- we have to find that there is substantial evidence of effectiveness for the effect on the surrogate.

So as I noted earlier, the sine qua non for approval is the finding of substantial evidence of effectiveness. And if we're contemplating utilizing the accelerated approval route, we still have to have substantial evidence of effectiveness for the surrogate.

As I just discussed, there are really only two ways to obtain substantial evidence of effectiveness, either with two adequate and well-controlled trials or one trial and confirmatory evidence. One of these standards has to be met for the effect on the surrogate for us to approve a drug under

subpart H or accelerated approval.

The reasonably likely standard applies to the question of whether or not that effect on the surrogate will result in a clinical benefit down the road, but the effect on the surrogate has to be supported by substantial evidence of effectiveness as the law defines it.

So as I said, FAP is an orphan disease. It's a relatively small orphan disease. And it's important for you to know, though, that the law actually makes no distinction between the evidence required to approve a drug for an orphan disease and the evidence required to approve a non-orphan disease. Specifically, we have to find that there is substantial evidence of effectiveness to support the orphan claim, just like we do for any other type of claim.

But having said this, it should also be said that there is considerable flexibility in how the standards are applied in any given case, both orphan or not orphan for that matter, and we are undoubtedly going to be discussing the sorts of flexibility built into the system a great deal today.

We are committed to applying as much flexibility as we can, but this has to be done within the requirements of the law. The law standards are designed to ensure, as much as possible, that only drugs that have been found to have the effects claimed for them are approved for marketing. The law presupposes, and I think appropriately so, that approving drugs that have not been shown to be effective is inappropriate. And I think that's a widely accepted premise.

I should note that it's possible under certain circumstances to make a drug more or less widely available, at least for some patients, before a drug is approved but while studies designed to demonstrate its effectiveness are ongoing; and we will be discussing these sorts of approaches later. But approval for marketing has to be based on a finding of substantial evidence of effectiveness.

With this background, I'll just turn to some of the issues, then, that we would like the committee to consider and are incorporated in our documents and in the question list that we sent you. Dr. Farkas will

be presenting later, and he will go into these issues in far more detail, but I just want to lay them out for you at the beginning.

Probably, perhaps, of primary concern for us is the finding that neither of the two outcomes prospectively designated in the protocol as primary yielded between-treatment contrasts that were statistically significant by the usual standard.

Specifically, the p value for the contrast on the NIS-LL, which is a measure of peripheral nerve function -- and the primary outcome was based on a responder analysis defined in a certain way -- that p value was .07. And the p value for the TQOL, which is a quality of life sort of global measurement, was 0.12.

Now, the sponsor notes that there were considerably more dropouts from this study than they planned on, and these dropouts or discontinuations were largely related to patients who received liver transplants. Most of these patients were on the transplant list well before the study started, presumably. And these transplants occurred when their names came up, and they are presumably unrelated to the

patient's treatment assignment or perhaps how they were doing in the study. And according to the sponsor, analyses accounting for these discontinuations yielded what we'd call nominally significant results of around .04 to .05.

These secondary analyses were prospectively described in the protocol, but strict adherence to standard statistical practice would suggest that when the primary outcomes don't reach statistical significance, which these didn't, it's usually inappropriate to perform subsequent analyses. And again, strictly speaking, if those subsequent analyses are performed, it's difficult, if not impossible, to really understand what the p values mean. A p value of .05 done after the primary outcomes were negative doesn't have the same meaning as a p value of .05 for the primary outcomes.

So in addition to the protocol-specified primary outcome of the NIS-LL, which was again a responder rate, the sponsor analyzed the change from baseline in the NIS- LL as a continuous variable, and there they also obtained a nominal p value of .03. Our

statistician, Dr. Luan, also performed a similar analysis of the NIS-LL as a continuous variable, but she excluded two placebo patients who were clearly outliers. And when that analysis was done, the result lost even nominal statistical significance.

In addition to Study 005, multiple secondary outcomes were assessed. These were all in the protocol, but there was no prospective statistical plan as far as we know to analyze these outcomes in any particular order. And for some of these between-treatment contrasts, for some of these outcomes, the between- treatment contrast was again nominally less than 5 percent. And the sponsor describes these analyses as being prospectively designated.

It's true. They were prospectively designated, but again, there was no formal statistical plan in place for analyzing these outcomes in a particular order. And as I noted, given the fact that there was no attempt to correct for multiple comparisons, no prospectively designated order in which these were to be treated, and given the fact that the primary outcomes were negative, it's very difficult to

understand what those p values mean.

I should also make clear that even if several outcomes are seen to be nominally statistically significant, whatever that means, the ones in the study are likely to have been fairly highly correlated with each other. So for this reason, the results of numerous analyses, which appear possibly to be significant on the face, although again they're nominal, cannot be considered to be analyses of entirely independent outcomes. And therefore, any attempt to consider these multiple allegedly nominally significant findings as providing independent replication of the sort we talked about earlier is very problematic.

There are several other issues of concern. We found that there is evidence of important differences at baseline between the two treatment groups. And in particular, several lines of evidence suggest that patients randomized to tafamidis were less impaired at baseline than those randomized to placebo. That just happened by chance. But we also found out that the ultimate responder status was actually dependent on the

baseline status. And when Dr. Luan performed an analysis accounting for these baseline differences, for the NIS- LL, I believe the responder rate, the p value increased from the .07, which was seen on the prospective primary outcome, to a .16.

The sponsor also examined the effects of baseline differences and found no effect of differences on the outcome. However, we believe Dr. Luan has shown that those analyses are highly dependent upon how patients were categorized at baseline. And these were categorizations, as far as we can tell, that were not described prospectively in the protocol, they were performed after the trial was done, and the results were known. Various other categorizations did not give consistent results.

Another concern arises from the fact that almost 60 percent of the patients were enrolled at a single center. Recall one of the criteria for the substantial evidence deriving from a single study, that the guidance document describes, is that no one single center provide all the positive results.

All of the apparent effect of the treatment

study-wide arose from this center, where it again needs to be noted that there appeared to be important baseline differences between the two treatment groups. In the other centers, which contained 40 percent of the patients in this study, no effect of the treatment was seen.

So as you know, the sponsor also performed Study 006. We don't believe this can be considered an adequate and well-controlled trial, but the sponsor does offer it as providing supportive evidence of effectiveness.

Again, although some of the contrast performed by the sponsor did reach nominal statistical significance, these results need to be considered in light of the fact that treatment was unblinded for all patients. There appeared to be no prospective plan for analyzing particular outcomes in particular orders. And the patients entered into 006 represented a non-randomized subset of patients enrolled in 005. And even so, the results don't appear to uniformly support an effect of tafamidis. So we're certainly interested in what the committee thinks about that.

So given these data and concerns, we're asking the committee if any of the standards for approval described earlier can be considered to apply in this case. Specifically and of paramount importance, we need to know if the committee can conclude that the sponsor has submitted substantial evidence of effectiveness for tafamidis as a treatment for FAP or to slow the progression of FAP.

Recall the two definitions of substantial evidence. we don't believe that the sponsor has submitted two adequate and well-controlled studies. So therefore, we're asking the committee if you believe that the sponsor has submitted a single, adequate, and well- controlled study plus confirmatory evidence that establishes effectiveness.

In this regard, recall that in a typical case that relies on a single study, that single study is typically robust with low p values, many different outcome measures and analyses yielding statistical significance and findings that do not arise from a single center. That's typically, anyway.

For such a standard to apply, a highly robust

single study could itself provide the necessary confirmatory evidence. Or the latter, again, could come from another source, in this case, perhaps Study 006, although as we've seen, we have concerns about the findings in that study.

Importantly, if you can't conclude that the one- study standard has been met for a clinical outcome, we need to know if you can conclude that this standard has been met for a surrogate that is reasonably likely to predict a clinical benefit. And as noted earlier, such a surrogate is typically a lab test, but it can be, as I said, a clinical outcome.

It's possible that one could consider some of the clinical outcomes assessed as serving as potential surrogates for purposes of accelerated approval, for example, the large fiber function outcome, the small fiber function, or the NIS-LL itself.

Again, it's important to remember that, first, the sponsor must submit substantial evidence of effectiveness for the effect on the surrogate. And so in this regard, the committee must find that substantial evidence of effectiveness has been

demonstrated for one or some of these outcomes before it can even be considered as the basis for approval under subpart H. And if the committee would consider this approach, we would need to know what ultimate clinical outcome you think the effect on those earlier outcomes would predict and what the evidence is for claiming that it would predict it.

Regarding other potential surrogates, it is worth pointing out that there seems to be an overwhelmingly clear effect of tafamidis on TTR stabilization, not only in Study 005, but in other open- label studies which enrolled patients who did not have the V30M mutation. They had other mutations.

Regardless of the mutations studied, the sponsor reports that almost all patients treated achieved stabilization of TTR. So a few words of clarification with regard to that finding are in order, I think.

As I noted earlier, TTR is in equilibrium with its monomers. The assay the sponsor used assesses, in effect, the speed of dissociation of the tetramer into the monomers. By stabilization of TTR,

as assessed by this test, the sponsor means that the rate of stabilization has been slowed compared to the baseline rate. It does not mean that the TTR has been completely stabilized. And the data from Study 005 suggests that the average slowing of the rate of dissociation is about two-and-a-half-fold slower than at baseline.

So when the sponsor reports that essentially all patients receiving tafamidis achieve stabilization, that's the average degree of slowing or dissociation that they achieved. And of course, that represents a distribution.

But as Dr. Farkas will go into in more detail, we have concerns both about the specific assay used to document the stabilization of TTR. For example, does it really represent -- given the conditions of the assay, does it actually represent stabilization of the tetramer in vivo?

But also, we have questions about whether an effect on this measure is, in fact, reasonably likely to predict a beneficial clinical effect. Recall that approving a drug under subpart H requires numerous

assumptions about the effects, good and bad, of the treatment and the pathophysiology of the disease. For example, whether this degree of stabilization will have any effect on the ultimate disability in patients with FAP or any effect at all on the formation and deposition of amyloid, which presumably is the ultimate cause of the patient's symptoms, isn't known.

We're of course very interested in knowing, then, if the committee believes the sponsor has submitted substantial evidence of effectiveness for a surrogate marker that is reasonably likely to predict a meaningful clinical benefit. And Dr. Farkas again will go into some more detail about the use of surrogates in this case.

If the committee cannot conclude that the sponsor has submitted substantial evidence of effectiveness for either clinical outcome or a surrogate marker that's reasonably likely to predict a clinical benefit, we need to know if the committee can conclude that Study 005 could serve as one adequate and well- controlled study that could contribute to a finding of substantial evidence of effectiveness if

combined with an additional study that might be performed in the future.

Finally, Dr. Farkas will describe what we believe are several potentially acceptable designs for additional clinical studies that the sponsor might be able to perform if we find that that is necessary. These designs would be capable, in our view, of efficiently answering the question of effectiveness of tafamidis while minimizing, to the extent possible, patients' exposures to an ineffective treatment.

One final word. As I wrote in my briefing memo, agency policy requires primary reviewers to make a recommendation about what action the agency should take on any new drug applications. And as you know, we've included several agency reviews with recommendations. I just, again, want to assure the committee that we have not made any final decision on this application. Clearly, we are coming to you today because we believe that we cannot make a final decision without your input and advice.

So with that introduction, I'd like to thank you for the work that you have done in preparation for

the meeting. Thank you in advance for the work you will be doing today. I'd also say that we gave you a question list. Of course, we are interested -- if there's something that is not on that list that you think is relevant, that we haven't brought up, we of course want to know what you think about that, too.

With that, I will hand the floor back to Dr. Fountain. Thank you.

DR. FOUNTAIN: Thank you. Dr. Chaudhry joined us.

Could I ask you to introduce yourself? We introduced ourselves earlier.

DR. CHAUDHRY: I apologize for coming late. I'm Vinay Chaudhry. I'm a professor at Johns Hopkins University School of Medicine, and I'm a peripheral nerve expert in neuromuscular diseases and see some patients with amyloid and other peripheral neuropathies.

DR. FOUNTAIN: Thank you.

We'll now proceed with the sponsor's presentation. Dr. Kahn?

MS. KAHN: Good morning, Mr. Chairman,

members of the committee, Dr. Katz, FDA, ladies and gentlemen. I'm Clare Kahn, vice president for worldwide regulatory strategy for specialty care at Pfizer. And on behalf of Pfizer, we thank you for the opportunity to discuss tafamidis today.

Pfizer recognizes the burden that rare diseases impose on patients in society and we are committed to finding innovative new treatments for patients with orphan and genetic diseases. So before I begin, I'd like to thank all the investigators and the patients who have participated in the tafamidis program.

The indications sought for tafamidis, trade name Vyndaqel, is for the treatment of transthyretin amyloidosis in adult patients with symptomatic polyneuropathy to delay neurologic impairment.

Transthyretin is a tetrameric protein synthesized in the liver that derives its name from its function as a tertiary transport protein for thyroxin and retinal binding complex. And transthyretin familial amyloid polyneuropathy, or TTR-FAP, is one of two major phenotypes of familial amyloidosis. The

other is cardiomyopathy, which is also known as TTR-FAC, and that's the subject of a separate development program.

So TTR-FAP is a very rare and fatal genetic disease caused by a mutation in the TTR gene, which renders the tetramer protein unstable. And it's this instability that's the rate-limited step in the amyloid cascade which develops into an irreversible and relentlessly progressive neurodegenerative disease. There's no pharmacological treatment available in the United States and the only option is liver transplantation to remove the source of the unstable protein.

Now, tafamidis is a small molecule specifically designed to bind the thyroxin binding site of TTR and serve as a selective stabilizer to block that rate- limiting step in the amyloid cascade, and slow the progression of disease. Stabilization of the tetramer is a biologically plausible biomarker for efficacy of tafamidis across our clinical program.

Meeting the unmet need in TTR-FAP is a story of bench-to-bedside drug development. You're going to

hear how a clinical observation of naturally protective genetic variance led to the elucidation of the molecular pathophysiology and a rational drug design focused on tetramer stabilization.

The clinical program tested the effectiveness of this approach based upon a single placebo-controlled trial with confirmatory evidence from supportive trials to seek approval and access for patients in the U.S. It's this program that supported approval last year in Europe under a provision called exceptional circumstances, which bears a commitment to obtain additional data in the more rare V30M non-V30M, I should say, variance using the THAOS registry in the post- approval setting.

THAOS is the only prospective disease registry for all patients with TTR amyloidosis, and it's been in effect since 2007, allowing us to study patients with all variants at all stages of disease, including pre- and post-transplant and those receiving tafamidis. And at this time, over 1,200 patients are participating globally, including in the U.S.

So there are no present trials for such a rare disease, so we engage in a thoughtful process of selecting endpoints validated in diabetic neuropathy, adding additional endpoints relevant to TTR-FAP. Clinical outcomes such as ambulation or mortality are less feasible, given the years it would take to study and the intervention of transplantation. And it's these outcomes that will also be addressed in the THAOS database.

So to support our indication, we used an array of mechanistic and clear clinical measures which sought to demonstrate replication of effect on very different dimensions of disease progression. And two co-primary endpoints taken together were to demonstrate the clinical benefit of how a patient feels or functions. Then a range of neurological and neurophysiological function measures were used to document disease progression and serve as clinical markers, which are reasonably likely to predict clinical benefit.

In this disease, where wasting is a key feature, the modified body mass index is not just a

nutritional measure, but has been shown to have prognostic value for outcome. And so if viewed together with all of the other measures, serves as an additional clinical marker. And of course, all of the effects were anticipated from the necessary stabilization of TTR, which underscores the program across the program and provides a biologically plausible marker by interruption of that first step in the amyloid cascade.

As I mentioned, the core to the program is a single double-blinded placebo-controlled trial, Study 005, conducted in patients with a common genetic variant, V30M. We acknowledge that the primary endpoint did not meet the pre-specified statistical criteria for the intent-to-treat population. However, as you will hear throughout the presentation, if permitted to examine the totality of the data, the weight of evidence across a variety of endpoints provides a strong support for the efficacy of tafamidis through stabilization of TTR.

Confirmatory evidence is derived from Study 006, which affords a second look at that same array of

endpoints, comparing patients continuing on tafamidis with those switched from placebo to tafamidis.

Generalizability of effect is supported by Study 201 in the non-V30M patients, the durability of effect, examined over two and a half years in this NDA, across Studies 005 and 006, and continuing in the ongoing study, 303, which captures all patients and some of whom who have exceeded five years now in treatment.

The tafamidis program is the first prospective drug development for TTR-FAP and has 187 patient years in 127 unique patients. The totality of the data from a single pivotal and supportive trial using clinical endpoints and biomarkers, together with an uncomplicated safety profile, provides convincing evidence of a positive benefit-risk that justifies making this medicine available to patients as soon as possible.

FDA has afforded fast-track and priority review, which is befitting of a serious orphan disease with unmet medical need, and this brings us to the committee today. For traditional approval, you would

need to consider the two co-primary endpoints, which is essentially the basis of question 2A. An accelerated approval is based on endpoints that are reasonably likely to predict clinical benefit, which is essentially the basis of question 2B.

Regardless of the approval pathway, Pfizer is committed to continuing the study of tafamidis in TTR-FAP. If accelerated approval is granted on the condition that clinical benefit is to be confirmed post-approval, Pfizer commits to conduct a feasible confirmatory efficacy trial. This would allow pts in the United States with this progressive condition to receive tafamidis treatment now without waiting for the completion of a new confirmatory trial.

Now, before we begin our presentation, I'd like to note that Dr. David Lewis from Tufts University, who's an expert on liver transplant, is here with us today.

Now, to our agenda. It's my pleasure to introduce Dr. Steven Zeldenrust from the Mayo Clinic, who will provide his clinical experience with TTR-FAP and its devastating effect on patients.

DR. ZELDENRUST: Thank you, Dr. Kahn.

Good morning. I'm Steve Zeldenrust, an assistant professor of medicine and a consultant in the division of hematology at the Mayo Clinic. I'd like to disclose that I am a paid consultant to the sponsor, but I have no financial interest in the outcome of today's meeting.

You may be wondering why a hematologist is here to talk to you this morning about a neurologic disease. My Ph.D. thesis focused on transthyretin amyloid, and I'm currently attending physician at Mayo Clinic, where we have a specialized treatment center for the treatment of amyloid within the division of hematology. And as a clinician primarily responsible for TTR-FAP patients, I see roughly 30 patients a year.

This hopefully gives you some idea of the extreme rarity of this disease, since we are considered one of the primary referral centers for this disease in the United States.

My reason for being here today is really quite simple. I hope to put a face on TTR-FAP. Most of you have likely never heard of this disease before

today and never seen a patient with it. So as a physician who cares for these patients, I hope to leave you with some idea of the problems they face and the limited treatment options that are available for them.

So what is TTR-FAP? It's the most common hereditary form of the rare, fatal, protein-deposition diseases we call amyloidosis. And you'll hear more about the pathogenesis of the disease from Dr. Kelly, but it's important to know that it's an autosomal-dominant disease with variable penetrants. And that means that 50 percent of the children of an affected patient can inherit the gene, but may not develop the clinical disease.

It's a highly diverse disease with over 100 different point mutations identified in a protein that only contains 127 amino acids. But despite that genetic diversity, the pathogenesis of the disease remains the same regardless of the mutation.

TTR-FAP is an extremely rare disease, with a U.S. prevalence estimated at fewer than 2500 patients. Given its rarity, it's frequently misdiagnosed. And as a result, as few as 350 people in total are currently

identified as having this disease in the United States. Worldwide prevalence is roughly two to four times that seen in the United States.

TTR-FAP occurs both endemically and sporadically throughout the world. And on the map you see here are clusters of patients that have been reported in various regions of the world. Three large circles represent endemic foci of the disease in Portugal, Sweden, and Japan. And these patients all share the most common V30M mutation, which is present in about 40 percent of U.S.

patients. As you'll hear, much of what we know about this disease comes from studies of these patients.

The smaller circles represent sporadic foci, found in the rest of the world, including the U.S. And these can either be large families that share a common mutation or often single families with a novel one.

TTR-FAP patients frequently develop symptoms in their 30s and 40s, in the prime of their lives, with irreversible progression, leading ultimately to death within 10 or 15 years from onset.

So what does TTR-FAP look like? As you might have gathered from its name, TTR familial amyloid polyneuropathy, the predominant feature of this disease and the one that's most relevant to today's discussion, is that of a degenerative peripheral neuropathy. Nerve function is affected in a link-dependent fashion, starting with the longest nerves in the body, typically those in the lower extremities. Initial symptoms are often fairly innocuous, some mild discomfort or numbness, usually in the toes. But this is followed by relentless progression involving the feet, then the legs, and ultimately the upper extremities. By the time patients have sensory involvement below their ankle, they begin to experience motor symptoms and weakness as well.

The process can take years, but progressively affects patients' ability to perform simple tasks like dressing, eating, and taking care of themselves. Within a few years from onset, the symptoms reach the knee, at which point patients are no longer able to walk on their own.

By this time, they have complete loss of

sensation in their feet, often suffering injuries they are oblivious to. They can no longer drive or work. They become totally dependent on others to care for them. They ultimately progress to become bedridden or wheelchair bound, where they're at risk for infections, pneumonia, and malnutrition, leading to death.

Patients frequently suffer from autonomic dysfunction as well. Autonomic neuropathy causes erectile dysfunction, which can be very distressing to a 30-year-old man. Orthostatic hypotension and syncope lead to difficulty standing and frequent falls.

GI involvement shows up as alternating diarrhea and constipation, which can be disabling, as patients can have up to 20 stools in a day. Many become incontinent and are afraid to leave their home as a result. Urinary retention leads to increased infections and requires self-catheterization, which can be extremely difficult when you can't feel your fingers.

Although we've been talking about the neurologic features of this disease, we can't lose sight of the fact that TTR-FAP is a systemic disease

and can involve other organs as well. And while not common in the V30M population, significant cardiac involvement is critical and can range from mild arrhythmias to cardiomyopathy and outright heart failure. The kidneys, eyes, even the central nervous system, can be involved in many patients, depending on the mutation that they carry.

Weight loss is another common feature that's often overlooked in the course of this disease. And while we don't know the exact etiology of the severe and progressive weight loss, autonomic dysfunction undoubtedly plays a major role as patients battle incontinence, gastroparesis, and impaired motility. Cachexia inevitably ensues and is a common cause of death.

These pictures were of one of my patients, shown in the two pictures on the left, prior to the development of symptomatic amyloidosis at a time when he was actually trying out as a lineman for the Minnesota Vikings football team.

The picture of him seated on the right was taken just before he underwent liver transplant, a

point at which he had unintentionally lost over 150 pounds. By this time, he had also developed profound sensory and motor symptoms as well.

So what can we do to help? The only available treatment option at present is liver transplantation. The vast majority of circulating TTR is produced by the liver. By replacing the patient's liver with one from a healthy donor, we can effectively remove the source of the amyloid.

Most of what we know about liver transplant comes from studying V30M patients, in which 80 percent of patients benefit, including a clear, long-term survival advantage. However, it's hardly a benign procedure. It has a 10 percent mortality risk in the first year and an overall 23 percent mortality risk by five years. Patients with non-V30M mutations do even worse, with a 44 percent mortality risk at five years, and can often develop progressive symptoms following transplant.

In addition to the risks of the surgery itself, patients need to be on lifelong immunosuppression, leading to increased infectious

complications. And as you can imagine, this is a daunting prospect for a 30- or 40-year-old to consider. And for patients that may have watched a sibling or relative die as a result of their transplant, you can see the fear on their face when they hear that this is the only treatment option available to them.

Of course, due to limited donor availability, not all patients accepting of the procedure actually undergo a transplant. Depending on the transplant center and the patient's blood type, the wait time may be a year or more. Those with cardiac involvement often need a combined heart-liver transplant, which adds significantly to both the risk and the wait time.

Even more worrisome than the surgery itself is the fact that not all patients benefit. It's clear from both the literature and from my own practice that some patients will continue to progress after a liver transplant, particularly those with cardiac involvement. It's been well-documented that continued production of wild-type TTR by the donor liver can participate in new amyloid deposits following liver transplant.

What about those who are waiting or are ineligible for liver transplant? Treatment for these patients is purely palliative. And while that's important for managing symptoms, none of these treatments alter the natural history of the disease or slow its progress.

So where does tafamidis come in? Despite the success of liver transplant, it's clear not everyone is eligible for transplant or benefits from it. We desperately need more treatment options for these patients, other than just palliative care.

You'll see some data today that suggests tafamidis may be helpful in filling that need, but some important questions remain to be answered.

What about patients with advanced symptoms? Is there a point of no return? Does tafamidis have a beneficial effect in cardiac involvement? And given the significant number of U.S. patients with cardiac involvement at the time of diagnosis, is a combined heart-liver transplant the only option for these patients? Is there a role for patients that progress after a liver transplant?

I think it's worth noting that TTR stabilization is really a novel paradigm in the treatment of this disease. Liver transplant simply substitutes wild type TTR for the mutant, but tafamidis and other TTR stabilizers have the ability to stabilize the wild type protein as well as the mutant. Clearly, more studies are needed to answer these questions.

So in summary, TTR-FAP remains a rare, relentless, and variable fatal disease which is challenging to both diagnose and treat.

The only currently available treatment option is liver transplant, which is an invasive procedure associated with significant morbidity and mortality and not an option for all patients. For those ineligible for transplant, palliative treatment is the only option.

TTR-FAP patients and the physicians who treat them, like myself, desperately and urgently need more effective treatments like the one being discussed today. And while there are still some unanswered questions regarding how tafamidis will fit into the treatment of TTR-FAP patients in the U.S., the fact is

patients continue to suffer and die while we wait for better treatments to become available.

Thank you.

Now it's my pleasure to pass the podium to Dr. Jeff Kelly, the inventor of tafamidis.

DR. KELLY: Good morning. I am Jeff Kelly. I'm chairman of molecular medicine and professor of chemistry at the Scripps Research Institute. I had the privilege of discovering tafamidis and starting FoldRX Pharmaceuticals. Thus, I would receive financial benefit from approval.

My role this morning is to tell you how, by uncovering the mechanism of aggregation of transthyretin, we were able to conceive of the kinetic stabilizer strategy and the molecule tafamidis, which is a kinetic stabilizer, which you'll see from the clinical data today slows familial amyloid polyneuropathy.

So I'd like to provide an introduction to the transthyretin amyloidosis briefly from the perspective of structural biology, and then talk about the kinetic stabilization strategy, and then some of the

experiments upon which the 20-milligram once-daily dose was selected.

So the liver biosynthesizes and secretes 95 percent of transthyretin that's in the plasma as a tetramer, which I'll have more to say about in a few minutes. The tetramer has to dissociate to a monomer, and the monomer has to misfold in order to self-assemble into a variety of structures, including amyloid fibrals. And there's compelling genetic and pharmacologic evidence that the process of amyloidogenesis causes these diseases. And as you heard from Steve, some of the mutants lead to a primary autonomic or peripheral neuropathy. And that will be the focus today. And other sequences of transthyretin lead to cardiomyopathy.

If you focus your attention on the left-hand side of this slide, 60 percent of the protein that's in your plasma is unliganded transthyretin comprised of four beta-sheet-rich subunits, as you can see. The remaining 40 or so percent is shown on the right-hand slide. This is transthyretin in complex with retinal binding protein, bound to vitamin A.

Thyroid-binding globulin and albumin carry the vast majority of thyroid hormone in our plasma. In fact, if you immunoprecipitate transthyretin and induce sophisticated LCMS analysis, in most patients you cannot detect thyroid hormone in transthyretin. So we're going to take advantage of the idea that these sites are unoccupied to kinetically stabilize the protein.

So in the next slide, this represents about 25 years' worth of mechanistic work. And I'd like to draw your attention to the second entry from the left. That is the naked tetramer, which is the most amyloidogenic form of transthyretin. But only after it dissociates first to a dimer, which rapidly falls apart to a folded monomer, it's only when the folded monomer changes its confirmation do you enter the neuropathological paradigm on the bottom, where the aggregation of the misfolded monomer into numerous structures, including amyloid fibrals, leads to pathology.

Now, we were very fortunate in our experiments showed that the weak link in this tetramer

is actually the dimer-dimer interface that comprises the small molecule binding sites. So you could imagine, if you created a small molecule that was neither a thyroid agonist or an antagonist, but bound in a very high affinity to that site, then you could stabilize the protein and lock it in its functional form, and preclude it from getting into the neuropathological mechanism.

Now, you're going to hear quite a bit about different mutations today, but really, for the purpose of today's discussion, this is very simple. They all destabilize the tetramer. As a consequence, they increase the concentration of the amyloidogenic monomer.

Remember, aggregation reactions are concentration-dependent. The higher the concentration, the faster the aggregation reaction. And of course, the faster the aggregation reaction, generally speaking, the earlier the onset of pathology.

So while we were busy using structure-based drug design to ultimately come up with tafamidis, Dr. Teresa Coelho, who you'll hear more from later, who has

the most experience with tafamidis and familial amyloid polyneuropathy from a clinical perspective, wearing her other hat as a medical geneticist, discovered three families in Portugal that are highly relevant to today's discussion.

So these individuals have the Val30Met polyneuropathy-associated mutation on one allele. On the other allele, they have a 3119Met mutation. Remember, this protein is a tetramer. So in these individuals, the tetramer is comprised statistically of Val30Met and 3119Met subunits.

So using E. coli, we were able to make the various tetramers shown here, comprised of both Val30Met and 3119Met subunits. And as you can see, as you increase the stoichiometry of the 3119Met subunits relative to Val30Met, both the rate of tetramer dissociation and the rate of amyloidogenesis plummets.

Now, Dr. Katz made a very interesting point in his introductory remarks today. Most proteins are in equilibrium and, thus, they exchange very quickly. The fact that we were able to isolate these different tetramers tells you that transthyretin is special. It

has a very high kinetic barrier for dissociation to begin with. And that point will become relevant again in a few minutes.

So if you focus your attention on the upper left-hand side of this slide, what you see is, as you increase the number of 3119Met subunits, you increase the barrier for tetramer dissociation. Effectively, the reason these individuals don't develop amyloidosis is that their tetramer is locked in a functional form because that barrier is insurmountable under physiologic conditions.

Now, if you focus your attention on the right side, the way tafamidis works is that it binds to and stabilizes the ground state of the tetramer, increasing the activation energy. So if you have a compound that binds with a dissociation constant like tafamidis, around two nanomolar, that makes that barrier insurmountable under physiologic conditions.

So you heard Dr. Katz mention a rate constant that was two or three times slower. That's in 5-molar urea. If you study this protein under physiologic conditions with tafamidis bound, it takes months to

dissociate. Okay? Again, it's a special protein, very high kinetic barriers.

So as I mentioned, we had the privilege of using structure-based drug design. In fact, structure-based drug design was invented with transthyretin. So we came up with tafamidis, which as you can see looks nothing like thyroid hormone. In fact, it doesn't displace thyroid hormone from the thyroid receptor.

So how did we select the 20-milligram dose? We selected the 20-milligram dose using an ascending or a dose escalation study where we monitored transthyretin's stability as a function of the tafamidis-to-TTR plasma ratio, as you see on the X axis.

So at 20 milligrams, the minimum concentration or the trough concentration occupies 1.2 of the two binding sites. That is sufficient to lock the protein in a tetrameric form kinetically. At Cmax, two binding sites are occupied. So again, this experiment is done by adding 4.8-molar urea to plasma so that you can monitor dissociation on a reasonable experimental time scale. It was never meant to use it

to extrapolate the rate constant to any kind of physiologic condition. If we want to do that, we have specific assays for that, which we can talk about in Q&A.

So if you now look at amyloidogenesis of the most important mutants of transthyretin -- Val30Met, you've heard of, polyneuropathy, V120II, cardiomyopathy -- you can see in the concentration range, from Cmin to Cmax, this small molecule effectively blocks amyloidogenesis over a 72-hour time period. That's highly relevant because this protein only lives in our plasma about 24 hours.

So let me conclude. TTR tetramer destabilization leads to amyloid fibrals and many other aggregates. Perhaps the most important conclusion from my remarks today are that tafamidis and the genetic mutation that Teresa Coelho discovered act in the same way. They kinetically lock the protein in a functional form and they don't let it enter the amyloidogenic cascade. And I told you about the experiments that we use to select the dose, and I also told you about the stabilization assay that we can talk more about later

if you'd like.

It simply remains for me to introduce Roy Freeman, professor of neurology at Harvard, who's going to tell you about the clinical metrics today.

DR. FREEMAN: Good morning. Thank you, Dr. Kelly. I am Roy Freeman. I am a professor of neurology at Harvard Medical School, and I direct the Center for Autonomic and Peripheral Nerve Disorders. I am a paid consultant to Pfizer, but have no financial interest in the outcome of this meeting. The goal of my presentation is to introduce the endpoints used in the tafamidis FAP program.

A few moments ago, you heard Dr. Kelly very eloquently describe the rational molecular pharmacology that underlies the clinical development of tafamidis. For me, as a clinical translational neuroscientist who's spent decades studying disease modification therapies for peripheral neuropathy, it is hard to imagine anything more exciting than this.

However, the introduction of tafamidis into the clinical arena imposed a set of challenges, specifically, how to quantify the neuropathy with

reproducibility and sensitivity with a disease-modifying intervention. Up until this point, there had been no prospective multi- center interventional trials, no validated clinical assessment tools, and no validated endpoints.

It was decided to draw on the instruments used in disease-modifying trials to treat diabetic peripheral neuropathy. Diabetic peripheral neuropathy, like FAP, is a length-dependent axonal neuropathy with sensory, autonomic, and motor features. The most widely used, best-validated, and most robust of the instruments used in diabetic peripheral neuropathy trials is the NIS, and specifically the NIS-LL, the Neuropathy Impairment Score of the Lower Limbs.

The NIS-LL is a validated structural neurological assessment tool. It is a subcomponent of the NIS specifically directed at the evaluation of the lower limbs, where the deficits in FAP occur initially. There is assessment of muscle strength, sensation, and reflexes. The lower limb score of the NIS-LL is from 0 to 88, where 88 is the greatest impairment. In individuals with diabetic peripheral neuropathy, the

NIS- LL increases by 0.9 points a year.

You will later hear from Dr. Donna Grogan that in FAP, there's a deterioration in the NIS-LL by .35 points a month, essentially a rate of change almost five times faster than seen in diabetic polyneuropathy. A consensus statement by the Peripheral Nerve Society proposed that a change of two points in the NIS-LL is clinically detectable and clinically meaningful.

With respect to the subcomponents of the NIS-LL, of greatest clinical and functional significance is muscle power testing. And with this instrument, all of the major muscle groups within the lower limbs are assessed. In brief, with progression proximally of the neuropathy, as ankle, knee, and hip weakness ensue, there will be substantial functional disability: ankle weakness, walking difficulties, knee weakness, instability even while standing, and hip weakness, resulting in wheelchair dependence.

Other subcomponents of the NIS-LL are the reflexes, which provide a general overview of nervous system function. And in addition, sensation is tested: pinprick, light touch, vibration, and

position sense. From a functional standpoint, vibration and position sense, the proprioception functions, are intimately involved with balance. Impaired proprioception will contribute to the walking difficulties.

The NIS-LL is corroborated by more objective neurophysiological measures, the nerve conduction studies, the standard neurophysiological assessment of the lower limbs: quantitative sensory testing, vibration perception threshold, code perception, and heat pain, and autonomic testing, heart rate variability, a robust measure of cardiac vagal parasympathetic function.

The results of these neurophysiological assessments are integrated into two composite scores, sigma 7 or the sum of 7, which you see on the left, which is a predominantly large fiber assessment, and sigma 3, seen on the right, a predominantly small fiber assessment.

Now, when used in disease-modifying trials for diabetic peripheral neuropathy, the NIS-LL has been used in three different ways. It's been used as a

continuous variable, addressing the total range of changes that occur with this assessment tool. It's also been used as a categorical variable, typically a responder defined as a change less than 2 points in the NIS-LL, as was done in clinical trial 005. And finally, it has been used as a composite score, combining both the NIS-LL itself with the more objective corroborating neurophysiological assessments.

In addition, a quality of life measure was used, the Norfolk Quality of Life, which is a widely-used and well-validated instrument in diabetic peripheral neuropathy. This is five domains, including large fiber, small fiber, and autonomic domains.

The modified body mass index was another endpoint in the clinical trial. This is the standard body mass index, corrected for serial albumin. You may recall there is malnutrition in familial amyloid polyneuropathy, in part due to amyloid deposition in the gastrointestinal tract, in part due to the autonomic neuropathy, causing diarrhea, resulting in malabsorption, diminished albumin, consequent edema, and the modified body mass index accounts for the

presence of edema. This correlates with disease severity, progression, and mortality in familial amyloid polyneuropathy and is a well-validated prognostic factor for predicting survival post-liver transplant.

I now want to introduce the clinimetric study. This study examines the question how applicable are these measures drawn from diabetic peripheral neuropathy to familial amyloid polyneuropathy, what is their diagnostic discriminatory ability across the disease stages of familial amyloid polyneuropathy.

The study was an observational, single-center, cross-section, non-interventional study, which looked at healthy volunteers and patients with various stages of familial amyloid polyneuropathy. The Coutinho staging system was used, which, in brief, cardinal features address ambulatory abilities. In stage 1, no assistance is required for walking; stage 2, assistance is required, and stage 3, wheelchair-boundedness occurred. All other neurological measures move in the same direction. The endpoints in the clinical trial were all assessed.

Looking at the primary efficacy endpoint, the overview of the structured neurological examination, the NIS-LL, as you see, differentiates with significance between healthy volunteers in stage 1, stage 1 and stage 2, and stage 2 and stage 3.

Now approaching the study from the standpoint of the progression of the peripheral neuropathy, as anticipated in the earlier stages, even the subclinical stages, neurophysiological abnormalities would occur. And here we see the neurophysiological tests, the composites, a score of 7, large fiber, a composite score of 3, small fiber differentiates between stage 1 and stage 2. And as anticipated, at the later stages of the disease, when the nerves are fairly severely damaged, you would not expect neurophysiology to differentiate between those stages.

Similarly, sensation involved earliest in the course of the disease, you see differentiation between healthy volunteers in stage 1, stage 1 and stage 2. With progression of the disease, reflexes will become involved, differentiation between stage 1 and stage 2, and ultimately, as muscle strength becomes impaired,

differentiation between stage 1 and stage 2, and stage 2 and stage 3.

Looking at this with a little more granularity, early in the course of the disease there will be toe weakness. And here, you see the instrument differentiates between stages 1 and stage 2. But with progression -- ankle weakness, knee weakness, and ultimately hip weakness -- the differentiation is strongest between the latter stages of the disease, hip weakness, stage 2 and stage 3; just what one would expect with a distal to proximal progressing axonal neuropathy.

Thus, in conclusion, these differences and patterns of deficits detected by the NIS-LL, the NIS-LL subscales, and neurophysiology discriminate among the disease stages with biological plausibility and are consistent with the clinical course of the disease. Although not shown, the total quality of life and the modified body mass index show similar diagnostic discriminatory abilities. Thus, these proposed endpoints are sensitive indicators of disease severity and are appropriate to measure disease-modifying

therapies in familial amyloid polyneuropathy.

I would now like to invite Dr. Donna Grogan to the podium to discuss the clinical development program for tafamidis.

DR. GROGAN: Thank you, Dr. Freeman. Good morning. My name is Donna Grogan and I am a physician consultant to Pfizer. As the former chief medical officer at FoldRX, I was responsible for the clinical development of tafamidis, and I would receive a financial benefit from its approval.

It is a real honor to be presenting the results of the years of research in this unprecedented program in this very rare disease. To address the questions posed to you today, I will be reviewing the tafamidis development program, including the efficacy and safety data from the pivotal trial, FX005, as well as data from the supportive studies.

Through the course of my presentation, I will be addressing many of the concerns raised in the FDA briefing document. Of note, we conducted a full clinical pharmacology program, the results of which are described in your briefing document.

As with many rare diseases, the tafamidis development program includes a single, well-controlled pivotal trial in patients with TTR-FAP. And this is due to the V30M mutation. The study represents the first prospective trial completed with a novel, investigational agent in this patient population. The pivotal trial was followed by a 12-month, open-label, single-treatment, extension study that provided us with additional and longer-term efficacy and safety data and also efficacy data in another group of patients, those previously on placebo.

In order to provide supporting data on the efficacy and safety of tafamidis in TTR patients with mutations other than V30M, we also conducted a 12-month open-label study in that population. And finally, we continue to monitor the safety and efficacy from the patients in our earlier trials through our ongoing label extension study 303.

Now, for a more detailed discussion of each of these studies, 005 was a standard double-blind design in which patients were randomized to tafamidis, 20 milligrams once daily or matching placebo for 18

months. This study was designed to enroll patients for whom a disease-modifying approach like tafamidis would be likely to show clinical benefit, that is, those patients who still maintain a relatively high degree of neurologic function to be preserved.

In addition, we enrolled patients with the V30M mutation because they represent approximately 85 percent of the worldwide population of patients with this disease and approximately 40 percent of the patients in the U.S. Although limited to the V30M mutation, we do believe the results are generalizable due to the similarities in neuropathic disease progression across mutations in TTR-

FAP.

The clinical endpoints in this study were those that measured different dimensions of this disease and are sensitive indicators of disease severity, as just described by Dr. Freeman. The first co-primary endpoint was the NIS-LL. For this endpoint, a categorical analysis was utilized, defining the NIS-LL responder as that patient with a less than 2 point increase at 18 months, based on a precedent trial in

diabetic polyneuropathy.

Importantly, patients who discontinued earlier to undergo liver transplant were categorized as non- responders. We believe this represents a conservative analysis, as unlike patients with chronic liver disease, TTR-FAP patients undergo liver transplant when an organ becomes available and not as salvaged therapy.

The second co-primary endpoint was the patient- reported outcome measure, the Norfolk Quality of Life. In addition to the categorical analysis of the NIS-LL, this continuous variable was analyzed as a continuous variable and as the pre-specified key secondary endpoint.

So in addition to the NIS-LL subscales, the Norfolk domains, other secondary endpoints assessed more objective measures of both small and predominantly large neurofunction and analyzed as submitted scores. The modified body mass index, this measure of overall disease severity, was also assessed. And finally, we assessed the effect of tafamidis on tetramer stabilization and the maintenance of this effect over

time.

These endpoints represent both clinical and biomarker assessments. No multiplicity adjustment was applied, as the co-primary endpoints were analyzed independently and a single key secondary endpoint was identified. This is not uncommon in the setting of this rare disease with the limited patient population. We specified two analysis populations, as described on this slide, the intent to treat and the efficacy evaluable.

Of the 128 patients randomized, 125 constitute the intent-to-treat population, with 87 making up the efficacy evaluable population. There was a low rate of discontinuation for adverse events, and the most common reason for discontinuation as liver transplantation.

The 20 percent dropout rate was evenly distributed between the treatment groups and was higher than the 5 to 10 percent expected rate of discontinuation assumed in the study design. But again, it's important to note that the majority of patients were on the liver transplant list at the time

of enrollment. And that liver transplant was performed not as salvage therapy, but when an organ became available. In fact, 73 percent of the patients who underwent liver transplant did so prior to the 12-month assessment.

So for any trials in rare disease, you have to go to where the patients are, and that is what we did in this trial. The enrollment proportions across sites, shown here in the middle column, matches the proportion of TTR-FAP patients who undergo liver transplant, as reported by the FAP World Transplant Registry on the far right column.

So although a single center provided slightly over 50 percent of the patients enrolled in this trial, this reflects real-world treatment of TTR-FAP and was thus by necessity. The Porto site represents the largest population of patients with this disease in the world and sees over 700 patients annually.

Now, baseline demographics demonstrated that patients were evenly divided between males and females, with an average age of 38 to 40 years. Placebo patients reported a mean disease duration of

approximately 12 months less than those on tafamidis. This mean difference appears related to a few outliers in a tafamidis group, with the median disease durations more similar between the groups.

But it's also important to understand that disease duration is a somewhat imprecise estimate and it is based on patient-retrospective recall of dates of symptom onset. In fact, over 50 percent of patients' start dates, either month or year, were not available for at least one TTR-related event. Therefore, definitive conclusions about the disease duration in either group are difficult.

The baseline disease characteristics demonstrate the relatively early stage of disease, with all patients fully ambulatory at the time of enrollment except for two patients, one in each treatment group. Thus, the endpoints used in this trial will show assay sensitivity in these early-stage patients, based on the data just shown by Dr. Freeman.

Although there were no statistically significant differences in disease characteristics, there were numerically higher NIS-LL scores in the

placebo group. In subsequent slides, you will see analyses that account for these numerical differences and why we do not believe these differences impact the overall interpretation of the study.

Now, for the primary endpoint results. Forty-five percent of tafamidis-treated patients were NIS-LL responders, compared with 29.5 percent of placebo patients, with a p value of 0.068. So while tafamidis showed a benefit, it did not achieve statistical significance. But it's important to remember that, in this analysis, patients undergoing liver transplant were categorized as non-responders. So the higher-than- anticipated dropout rate may have adversely affected our ability to demonstrate a statistically significant difference between the two treatment groups in this analysis.

Placebo patients experienced a non-significant worsening in mean total quality of life score at 18 months compared with tafamidis. It is important to remember that, as a disease-modifying treatment, tafamidis does not afford symptomatic benefit, and so we don't anticipate improvement in

symptoms or signs, but rather stabilization.

Now, when these same endpoints are evaluated in the efficacy evaluable population, those patients completing the full 18 months of treatment per protocol, there are significantly more NIS-LL responders in the tafamidis group compared with placebo, 60 percent versus 38 percent, with a p value of 0.041. And in this population, patients on placebo demonstrated significant worsening in total quality of life score compared with tafamidis patients, who had virtually no change in this score.

Now, in order to evaluate the potential impact of the baseline differences between the treatment groups, the responder analysis was assessed using different categories of NIS-LL. We performed this analysis in the efficacy evaluable population, as demonstrated on the slide, with the baseline categories of less than 4, 4 to 8, and greater than 8. In this analysis, the effect of tafamidis was evident in those patients who are more impaired at baseline.

Now, the FDA, in their briefing document, performed additional analyses using different

categories. These figures represent the data provided by the FDA statistical reviewer briefing document figures 10 through 12, formatted to show the percent response by treatment group, by NIS-LL severity baseline category.

The bottom left is the below and above median of baseline NIS-LL scores. The upper right is the below quartile, between lower and upper quartile, and above upper quartile. And the bottom right is within each quartile. But regardless of the method of categorizing baseline NIS-LL, we see a higher rate of NIS-LL responders in tafamidis-treated patients compared with placebo in the more moderate to more severe categories of patients enrolled in this study.

These results suggest that, for this categorical analysis of the NIS-LL, the baseline imbalance did not adversely affect the overall interpretation of the results, which is that more patients on tafamidis were NIS-LL responders than those on placebo.

Now, when the NIS-LL, this continuous variable, is analyzed as a continuous variable, we see

statistical significance between the treatment groups. The pre- specified key secondary, using a repeated measures analysis, demonstrates that tafamidis patients had significantly less worsening in NIS-LL at month 18 compared with placebo patients. This difference represents approximately 50 percent less decline in neurologic function in those patients treated with tafamidis.

This figure on the right is a post hoc analysis that incorporates baseline NIS-LL disease severity scores in the model. And as you can see, statistical significance is maintained.

The FDA noted that there were two outliers in the placebo group. And when these two patients were excluded from the ITT population, statistical significance in this analysis was lost.

The data from these two patients, as in all patients in our trial, were confirmed with the site as valid data and truly and accurately representing the progression of these patients. So although they were more rapidly progressing, it accurately reflected their course.

So to preserve the information provided by these two patients, we would argue that an alternative method might be preferable. In this method, their values were not excluded, but rather replaced with the values from a patient who had the next highest values in the dataset. The results, which are demonstrated on the right-hand panel, remain statistically significant and are similar to what we observed in the key secondary analysis, reproduced on the left.

So in summary, the NIS-LL change from baseline remains statistically significant across analyses and methodologies. First is the pre-specified key secondary analysis, using the MMRM method. Second is the same analysis, but with an adjustment for baseline NIS-LL severity. Third is the alternative method of dealing with the two placebo outlier patients. And last, although the data not graphically displayed, is the method using a multiple imputation method of dealing with missing data. Two of these analyses, the second and the fourth, were performed based on requests from the European authorities.

As you can see, across all of these analyses,

tafamidis patients had significantly less worsening of NIS-LL compared with placebo patients.

Now, let's delve into the NIS-LL in a little more detail. When we look at the components of this score, we see numerical advantages across the subscales in the tafamidis group. However, placebo patients experienced significantly more muscle weakness compared with tafamidis. And of course, worsening motor function would be expected to put the patients at a higher risk for development of ambulation abnormalities over time.

An even more detailed review of the motor subscale reveals that the tafamidis group demonstrated stability in muscle strength across the four major muscle groups of the lower limb, but in contrast, the muscle weakness in the placebo group occurred in this distal to proximal fashion, as would be expected for a length- dependent neuropathy. These results provide compelling evidence of the positive treatment effect of tafamidis and is supportive of the differences observed between the treatment groups in the NIS-LL responder analysis.

So finally, what about the influence of the high-enrolling site, Porto, on the analysis of the NIS-LL? We explored this question using the continuous change analysis of the NIS-LL across sites, in contrast to the analysis performed in the briefing document by the FDA, in which pooling was performed across the sites other than Porto in evaluating the responder analysis.

First to note is that there was a lower dropout rate due to liver transplant in the Porto site, 12.5 percent, compared with all other sites combined, 32 percent. This probably reflects the longer wait time on the liver transplant list due to the large volume of patients in Porto, but it also demonstrates that there is less missing data from this site, supporting the strength of the data results.

This bi-site analysis suggests that, except for two sites, Brazil and to a lesser extent Argentina, the results favored tafamidis in those sites with sufficient data at 18 months.

Now, similar findings were also observed in this bi-site analysis in the more objective measure of

large fiber function, the summated 7 score, again favoring tafamidis across the majority of sites. And similar findings were also found with the modified body mass index and the summated 3 scores, so these analyses further support the overall interpretation of the effect of tafamidis, regardless of geographic location or site.

Now, for the neurophysiologic measures. We see similar treatment effects to what was observed with the NIS-LL. In these analyses, tafamidis-treated patients demonstrated approximately 50 percent preservation of large fiber function compared with placebo, and this is consistent with the 50 percent preservation observed with the NIS-LL. For the small fiber function, treatment with tafamidis was associated with approximately 80 percent less deterioration, compared with placebo.

Tafamidis treatment was also associated with significant improvement in the modified body mass index, compared with worsening seen in the placebo patients. This assessment of overall disease severity suggests an overall greater disease progression in the

placebo patients.

Now, you will recall Dr. Kelly's hypothesis that a clinical benefit could be achieved through TTR stabilization by inhibiting amyloid fibral formation. Greater than 97 percent of patients on tafamidis exhibited TTR stabilization throughout the course of the study. And this stabilization translated into the clinical effects just described. These results support the use of TTR stabilization as a biomarker that is reasonably likely to predict clinical benefit.

Now, despite the challenges of conducting a prospective trial in this rare, fatal, neurodegenerative disease with limited patients, the pivotal trial, we believe, provides evidence that stabilization of the tetramer by tafamidis translates to beneficial effects across the array of clinical measures that were utilized in the trial.

On this slide, we are displaying the point estimates in 95 percent confidence intervals for each endpoint. Across all of these endpoints, which assess again different dimensions of this disease, a beneficial effect of tafamidis is observed. The

directional consistency provides internal replication and evidence for the overall benefit of tafamidis in this disease.

I would now like to describe the results of the 006 study, the open-label extension trial. Following completion of the double-blind trial, patients were enrolled in this extension study and all received 20 milligrams, tafamidis, once daily. The objectives included the assessment of safety as well as the evaluation of efficacy, using the same endpoints as the previous trial. You can see from this diagram that these trials provide data on 30 months' continuous treatment with tafamidis for those patients on tafamidis in the double-blind trial and 12 months' data for those patients previously on placebo. The blind from the pivotal trial was maintained during the open-label extension for both patients and physicians.

Eighty-six of the 91 patients who completed 005 continued into this open-label extension with 77 completing the 12-month treatment period. Six patients discontinued due to liver transplant, so a much lower rate than what we observed in the double-blind trial.

The intent-to-treat population includes 38 patients in the tafamidis-tafamidis group. And that group is those patients who received tafamidis in both the double-blind trial and the open-label extension, and 33 patients in the placebo-tafamidis group, those patients who received placebo in the double-blind trial, and then tafamidis in the open-label extension.

The baseline demographics for the study were similar between the tafamidis-tafamidis group and placebo-tafamidis group, with median disease durations of approximately 36 months. However, baseline disease characteristics demonstrate that the placebo-tafamidis group has significantly worse NIS-LL, quality of life, and summated 3 score, with numerically worse sum 7 and lower BMI.

This is not surprising, given the observed progression in disease which occurred in this group during the previous 12 -- 18 months of placebo treatment. But these patients remained at a stage of disease within the range of endpoint assay sensitivity and remained ambulatory. And many of these analyses that I'll show you is a within-treatment-group

analysis.

So on this slide, as I mentioned, we performed a within-group analysis of the monthly rate of change during the double-blind trial compared to the open-label extension. And what we can determine from doing that analysis is twofold: one, whether the effects of tafamidis persist during the 12 months of open-label treatment in those patients who were on tafamidis for the full 30 months and whether tafamidis slowed disease progression in those patients previously on placebo.

So in the tafamidis-tafamidis group, as expected, the monthly rates of change were similar between the two studies and, again, consistent with the sustained treatment effect of tafamidis. And this is in contrast with the monthly rate of change observed in the placebo-tafamidis patients while they were on placebo in the previous double-blind trial, which is three times that of the tafamidis-tafamidis patients.

However, once the placebo patients switched to tafamidis, there was a statistically significant decrease in their NIS-LL rate of changed compared to

their rate while on placebo in the previous trial. In fact, this rate of change is now approaching the rate observed in the tafamidis-tafamidis group.

This is very supportive data on the impact of tafamidis in slowing disease progression, even for those patients with more severe disease at the time of tafamidis initiation. And in addition, it provides further evidence that the benefits observed in 005 were the results of a tafamidis treatment effect rather than any baseline differences.

A similar rate of change analysis was performed for the quality of life score. In the tafamidis- tafamidis group, the total quality of life rate of change from baseline was minimal and similar between the first 18 months of treatment with tafamidis and the following 12 months.

However, for the placebo-tafamidis group, there was a statistically significant decrease in their rate of change in quality of life while on tafamidis, compared with their prior treatment with placebo. And this actually resulted in a maintenance in their quality of life in these patients upon initiation of

tafamidis.

Similar findings are observed in the neurophysiologic measures of large fiber function on the top left and small fiber function on the bottom left, with slowing of rate of progression in these endpoints in the placebo-tafamidis group upon initiation of tafamidis. These data confirm the findings on the NIS-LL shown previously.

Although the sum 3 rate of change on the bottom left in the tafamidis-tafamidis group increases slightly, the absolute change observed over the 30 months of treatment is still less than that observed in the 005 placebo group after 18 months untreated.

Finally, upon initiation of tafamidis, those patients previously on placebo exhibited improvement in their modified body mass index. This is not unexpected and has been reported in patients post-liver transplant.

NIS-LL responder status was maintained over time. This slide displays the NIS-LL responder rate over the 18 months of double-blind trial in the first three sets of bars and the 12 months open-label trial

in the last two sets of bars. Fifty-five percent of the patients in the tafamidis-tafamidis group remained NIS-LL responders at month 30, again, less than 2 point change in the NIS-LL, further supporting the sustainability of the effect of tafamidis treatment. And in those patients previously on placebo, upon initiation of 12 months of tafamidis treatment, 60 percent of those patients had no disease progression.

Finally, the high proportion of patients with tetramer stabilization was maintained in the tafamidis-tafamidis group, similar to what was observed in the 005 study. And stabilization is now demonstrated in the placebo-tafamidis patients, which, as we've shown, translates to slowing in disease progression across the endpoints just described.

So in summary, the treatment benefits with tafamidis were maintained over 30 months, with over 50 percent of patients experiencing no disease progression, as assessed by the NIS-LL responder analysis.

Patients who had been on placebo had a slower rate of disease progression across the array of

endpoints upon initiation of tafamidis treatment. And these data do provide internal replication of the effect and serve as a source of confirmatory evidence of the efficacy of tafamidis.

To provide support for the use of tafamidis in patients with mutations other than V30M, an additional 12-month open-label study was performed, 1-A-201. In this study, the primary endpoint was TTR stabilization, with secondary endpoints similar to those in the previous trials.

The study was conducted in patients with eight different TTR variants and was intended to evaluate the stabilization of TTR across multiple mutations in order to assess a generalizability of tafamidis treatment effects. Twenty-one patients were enrolled in four countries, including the U.S. Patients were older, had longer disease duration, and had more advanced disease than the patients evaluated in Study FX005.

Consistent tetramer stabilization was seen and was demonstrated in all patients across all TTR mutations. The clinical endpoints used in this trial,

as I mentioned, were similar to those used in the previous trials. The change from baseline to month 12 for the patients enrolled in the 1-A-201 study, these non-V30M patients, are displayed in the second column. For comparison, the 12-month data by treatment group from the FX005 study are displayed in the last two columns.

So despite having more severe disease at baseline, changes from baseline on the efficacy endpoints were similar to changes observed in the FX005 treatment group and were less than that observed in the placebo group.

So in summary, TTR stabilization was demonstrated across all mutations evaluated in this study, and these findings, along with the clinical results, support the generalizability of tafamidis treatment.

So to conclude our discussion of efficacy, let me summarize. In the single pivotal trial, although the co-primary endpoints were not met, the totality of evidence and consistency in response across these multiple endpoints that measured different

aspects of this disease provide internal replication of the effects of tafamidis in delaying neurologic impairment in patients with TTR-FAP.

Tafamidis-treated patients experienced 50 to 80 percent preservation of neurologic function, as measured by the NIS-LL in neurophysiologic measures, less overall disease severity, and consistent stabilization of the tetramer.

The results from the single pivotal trial are supported by confirmatory evidence of efficacy from the supportive studies, in which we demonstrated maintenance of the effect of tafamidis for over 30 months, slowing of disease in those patients previously on placebo, thus replicating the FX005 treatment effect, but in a more severe population, and consistent TTR stabilization across all mutations.

Therefore, we conclude that the totality of the data support the original hypothesis that drove this development program, that stabilization of the tetramer by tafamidis does translate to slowing of disease progression in patients with TTR-FAP.

We just completed the review of the efficacy

data. And now, I will review the clinical safety data, the other side of this benefit-risk question. Please note that we have a full non-clinical safety program that's described in your briefing document.

The clinical data are derived from the clinical patient studies just described; 127 unique patients were treated with tafamidis. The accrued exposure is graphed on this slide in six-month increments. The median exposure is 35 months and 30 patients have been treated with tafamidis for more than four years. These data represent approximately 351 patient years of exposure. For the safety presentation, I will focus on the double- blind trial.

Few patients discontinue the study due to AEs, four from the tafamidis group and three from the placebo group. The adverse events that led to discontinuation in individual patients are noted on the right-hand side.

The majority of patients in both treatment groups reported at least one adverse event. The majority of adverse events were assessed as mild or moderate in severity. Those AEs reported more

frequently greater than or equal to two patients in the tafamidis group are highlighted, with the most common being diarrhea and urinary tract infection.

There were few serious adverse events reported. Six tafamidis patients and five placebo patients experienced at least one SAE. In those on tafamidis patients, they were related primarily to infection. All were successfully treated and resolved.

In Study 005, there were no deaths that occurred while on treatment. Five deaths were reported post-liver transplant, two of those patients previously on tafamidis and three previously on placebo. No deaths were reported in Studies 006 or 1-A-201. And four deaths occurred in Study 303, but none were considered to be related to treatment.

Now, to further assess the observed imbalance in urinary tract infections, we did the following analyses. We found that there was a higher ratio of women in the tafamidis group who had UTIs compared to placebo patients. However, in both groups, the majority of cases were mild to moderate, were successfully treated, and resolved, or were resolving.

There were not discontinuations from the study due to UTIs and no association between low white cell counts, neutrophils, lymphocytes, or any association with parameters in these patients who had infections.

A look at these additional safety topics revealed no evidence of adverse treatment effects caused by tafamidis, including extensive monitoring of thyroid function, liver function test, blood pressure, and heart rate, and ECGs.

Based on the totality of the safety data across the clinical program, it was determined that there are four AEs for which there is a basis to believe there is a causal relationship between their occurrence and the use of tafamidis. These AEs are identified as adverse drug reactions, as noted on this slide, and are proposed to be included in the product label.

Now, recognizing that safety data in this application is limited due to the rarity of this disease, we will continue to collect safety data in the post- marketing setting, using the tools as described on this slide.

So in closing, tafamidis was generally well tolerated in clinical trials, with a low discontinuation rate due to adverse events. And many of these AEs observed are consistent with disease morbidity. The identified risks are manageable and acceptable in the context of this disease and ongoing safety data are being collected.

So I hope I have provided you with an understanding of the scope of the efficacy and safety data included in this application. I now would like to invite Dr. Teresa Coelho, the principal investigator at Porto, who will provide a clinical perspective on TTR-FAP.

DR. COELHO: Thank you, Dr. Grogan. Good morning. I am Teresa Coelho. I am a neurologist and a neurophysiologist from Porto, Portugal, where I have treated FAP patients for 25 years. I'm a consultant to the sponsor and I was an investigator in the clinical trials. My institution was paid per protocol, but I have no financial interest in the outcome of this meeting.

Porto and my hospital in particular is where

the disease was discovered 70 years ago. Portugal is the most important endemic region in the world. In some districts north of Portugal, the prevalence of the disease is higher than 1 patient per 1,000 inhabitants.

San Antonio Hospital houses the largest clinic in the world. We follow 700 patients and 300 carriers every year, and we diagnose around 80 to 100 percent new patients every year. So it's not surprising that half the patients on the world FAP liver transplant registry are from Portugal.

In my practice, I have treated more than 70 patients with tafamidis. I have 44 patients currently on treatment, including 22 for almost five years and 22 for three and a half years. My experience so far has been that the majority of patients are stable. They are all in stage 1 and fully ambulatory. In fact, 41 out of the 43 patients were on the liver transplant waiting list. We drew their names from the list voluntarily. The patients and doctors agree that they were stable enough and will continue to be closely monitored.

FAP is a heterogenous condition. Even in an

endemic area like Portugal, we see heterogenicity. We have diagnosed families with non-Val30Met mutations. The age of onset varies between 20 and 80 years, and we follow a significant group of late onset patients. We have several patients with additional organ involvement beyond neuropathy.

Despite this variability, the neuropathy characteristics and the pattern of progression is similar across sites and mutations. The pathogenesis is the same, as you heard from Dr. Kelly. It's always a length- dependent neuropathy with sensory, motor, and autonomic involvement, with a severe progression invariably leading to a fatal outcome. For patients who present with neuropathy, life expectancy is consistent in different foci. That's why I believe tafamidis data may be generalizable to the U.S. patient population.

As someone who has treated patients for so many years and saw liver transplant as the first hope, I am excited about an option that does not have the additional complications associated with liver transplant.

Thank you for your attention. And now, I would like to invite Dr. Ilise Lombardo to the podium to present the benefit-risk profile of tafamidis.

DR. LOMBARDO: Thank you, Dr. Coelho.

My name is Dr. Ilise Lombardo, and I'm a physician with Pfizer, and I lead the worldwide medical and clinical efforts to register tafamidis for the treatment of TTR-FAP. At this time, I am going to summarize the data you've heard, which will be the basis for your evaluations of the questions, specifically whether these data provide substantial evidence of the clinical effect of tafamidis.

In the spirit of the Orphan Drug Act and per the FDA guidance, it's been noted that the broadest flexibility is afforded in applying the statutory standards for substantial evidence of efficacy in light of the nature and severity of this very rare disease. Of course, the appropriate assurances of both safety and effectiveness must be met. But we believe the totality of data that we have presented today meet that standard for tafamidis.

As you've heard, there are two pathways for

approval, traditional approval and accelerated or subpart H approval, which differ based on the type of endpoints used to demonstrate substantial efficacy. Traditional approval requires the demonstration of substantial evidence of efficacy on a clinical endpoint. And that's what you're being asked to consider for tafamidis in question 2A.

Subpart H or accelerated approval, which we believe is more appropriate for tafamidis, also requires the demonstration of substantial evidence of effect. However, this evidence of effect can be shown by either a clinical endpoint or biomarker that has not been formally validated, but is reasonably likely to predict clinical effect. That's what you're being asked to consider with question 2B. And in this case, confirmation of this clinical effect is then demonstrated in a confirmatory study in the post-approval setting.

I'd like to remind you that, as noted by FDA in their briefing document, clinical benefit is determined by tafamidis's effect on the NIS-LL and the TQOL, while the secondary clinical endpoints may all be

considered measures of disease progression likely to predict clinical benefit. In addition, TTR stabilization is a biologically plausible marker that's reasonably likely to predict clinical benefit.

So the co-primary endpoints, the NIS-LL, and the Norfolk TQOL, when considered together, are appropriate clinical endpoints by which we can assess tafamidis's efficacy as outlined in question 2A. Now, as discussed, the primary analysis of the co-primary endpoints on the left favor tafamidis, but did not meet statistical significance. However, for a disease-modifying approach, observation time is crucial to allow for the natural progression of disease. And due to the large and early dropout from liver transplant, the efficacy evaluable population is a relevant analysis by which to examine the treatment effect for tafamidis. And we did reach clinical statistical significance on each co-primary endpoint in this population.

Further, and as Dr. Grogan showed, the statistically significant change from baseline to month 18 for the NIS-LL further supports the effect of

tafamidis on neurologic function. These data provide evidence for the effect of tafamidis on the clinical endpoints outlined in 2A.

The secondary endpoints measured disease progression across multiple aspects of TTR-FAP and these formed the basis for the assessment of evidence in question 2B, to determine substantial evidence for a biomarker endpoint reasonably likely to predict clinical benefit.

Given the large number of unknowns as we entered into this program, we intentionally included measures examining different aspects of disease progression. Including this many different measurements was a development risk. If they didn't all line up, the results would have been very difficult to interpret. But when they all point in the same direction, they provide internal consistency and a source of replication of effect.

These are measures of disease status over time and, by their very nature, are reasonably likely to predict clinical benefit. And the consistency of findings favoring tafamidis across all of these

independent measures provides confidence that these data are in fact reflective of a true clinical benefit for tafamidis in the treatment of TTR-FAP.

As we look at these endpoints, especially the sum 3, the muscle strength, and the mBMI, we can say with confidence that the endpoints changed and that these endpoints are reasonably likely to predict clinical benefit. Also, the sum 3, sum 7, and mBMI correlate with the co-primary measures of clinical benefit.

In addition, the open-label study 006 provides us an opportunity to further examine tafamidis's treatment effect. Here, we see the rate of change analyses that were shown by Dr. Grogan, but for the placebo-tafamidis patients across the different endpoints.

Through examination of placebo patients, shown in gray, when crossed over to active treatment, shown in light blue, we see confirmatory evidence of tafamidis's clinical benefits. All measures demonstrated statistical or directional showing of disease progression in this patient group.

So in summary, the totality of evidence across secondary endpoints within the 005 study and the 006 study demonstrates consistency and replication. And these findings provide substantial evidence of effect on multiple endpoints reasonably likely to predict clinical benefit.

The consistency of these findings makes sense, given the mechanism of action of the drug. As you heard from Dr. Kelly, TTR dissociation is the rate-limiting step in the pathophysiology of TTR-FAP. And TTR stabilization, which correlates with amyloid fibral inhibition, is a plausible biomarker reasonably likely to predict clinical benefit. In our program, we demonstrated that tafamidis stabilizes TTR, and then this translates into the clinical effects we've seen in both Study 005 and 006.

These data, along with the stabilization of mutations other than V30M, support the generalizability of these results across mutations in this very rare disease, including those seen in the U.S. patient population.

Now turning to safety, the development

program characterized an acceptable safety profile for tafamidis, especially in light of the irreversible neurodegeneration and ultimate fatality of TTR-FAP. The safety profile was similar across treatment groups with respect to common adverse events and discontinuation rates due to AEs and SAEs. The adverse events seen in the tafamidis-treated patients were generally mild and manageable.

We believe the risk of approving tafamidis, given the above safety profile, is low compared to the risk of patients with TTR-FAP of having no approved treatment available. Currently, the only available option is liver transplant. While it is a valuable treatment for some patients, it's an invasive procedure with significant mortality, morbidity, and lifelong immunosuppression.

Tafamidis would be the first pharmacologic treatment option and the only option available to patients immediately upon diagnosis. While on tafamidis, patients could continue to be evaluated for progression or assessed for liver transplant according to current standards of practice.

As with any rare disease, we recognize there remain unanswered questions. A main source of new data generation will be through the THAOS disease registry, which we established five years ago to collect data on clinical outcomes which require observation periods too long for randomized controlled trials. Participants include patients with TTR-FAP who are untreated, treated patients with tafamidis, and those post-liver transplant. THAOS also collects data on patients in their related disorder, TTR cardiomyopathy, as well as asymptomatic genetic carriers.

THAOS is the ideal data source for examination of clinical benefit of long-term, real-world outcomes, and we will routinely make these data available for regulatory review.

Now, we note from the FDA's slides that potential expanded access is proposed as a means to make tafamidis available for patients. However, expanded access is not a substitute for product approval. Subpart H approval is the only sustainable model for making tafamidis available for patients as soon as possible. If, after these proceedings, subpart

H approval is granted, Pfizer will conduct an additional confirmatory study in the post-approval setting.

There are a range of options that we've discussed with FDA for a confirmatory study. These include utilizing the well-established THAOS registry, open-label treatment versus a historic control, the potential of another double-blind placebo-controlled study, or a study in TTR cardiomyopathy. FDA has indicated that a placebo-controlled trial is the preferred option. And while these studies will take time to complete, they are feasible.

The tafamidis clinical development program presented today contains the only control data from completed prospective studies in this orphan disease. The primary endpoints provide evidence for clinical effect of tafamidis and the secondary endpoints, which match what we understand of the underlying pathophysiology of TTR-FAP, are reasonably likely to predict clinical benefit.

There is convincing evidence to conclude a positive benefit-risk for tafamidis, given the

meaningful impact on delaying disease progression and the totality of the efficacy data, along with a manageable safety profile. We believe the benefits of tafamidis outweigh any potential risks.

As we conclude our presentation, I want to remind you of the degenerative and progressive nature of this disease that typically affects patients in the prime of their lives. They face catastrophic clinical consequences. They must either undergo liver transplantation or face a protracted course with progressive and substantial disability, ultimately succumbing to the disease, typically dying within 10 to 15 years of the first onset of symptoms.

TTR-FAP patients in the U.S. desperately need a treatment option. There will be opportunities to collect further data on the clinical effect of tafamidis, but this will take time. We ask that approval for tafamidis be considered based on the benefit-risk profile demonstrated in the current data package to make this treatment fully available for U.S. patients now.

Thank you for your consideration and we'll

look forward to your questions.

DR. FOUNTAIN: Thank you. Now we move to the clarifying questions. Are there any clarifying questions for the sponsor? And again, please remember to state your name before you speak.

(No response.)

DR. FOUNTAIN: Maybe I'll take the option of asking the first question.

Can you comment on whether or not cardiac effects were monitored during this study or if there are other aspects of familial amyloid cardiopathy that were considered during the course of the FAP studies?

DR. LOMBARDO: So to comment on the cardiac monitoring during the study, I'm going to call Dr. Donna Grogan.

DR. GROGAN: Cardiac effects were monitored, including ECGs and echocardiograms. But it's important to note that in these patients with the V30M mutation at this relatively early stage of disease, very few of them had cardiac involvement. In fact, there was very little -- no progression along the cardiac parameters even in the untreated population.

DR. FOUNTAIN: Thank you. Dr. Cohen?

DR. COHEN: So as someone who doesn't have the experience that's in Portugal, that has taken care of these patients, the major disabilities are the autonomic disabilities as well as the sensory disabilities. When I was looking at those data, what seems to be most important in your study is the muscle weakness, as far as disability factors. It occurs later in disease, so kind of help me with this.

DR. LOMBARDO: So Dr. Grogan can come up and speak to the effects in the 005 study.

DR. GROGAN: Yes. I think the data that we observed, even at the baseline data for these patients enrolled in our trial, does demonstrate that they have both a small fiber neuropathy, as noted by the summated 3 score, as well as a large fiber neuropathy, as demonstrated by that summated 7 score.

Although you are correct, the muscle weakness is the subscale which differentiated between the treatment groups, again, this was related to the placebo patients having greater progression. There were numerical differences between the treatment groups

in the other subscales, that did not achieve statistical significance.

DR. FOUNTAIN: Dr. Rosenberg?

DR. ROSENBERG: TTR stabilization certainly has face validity as a plausible mechanism of drug action. How are you proposing it as a surrogate endpoint? How does it fit in logically?

DR. LOMBARDO: Sure. Actually, I'd like to ask Dr. Kelly. Could you come up and please speak to the TTR stabilization?

DR. KELLY: So our thinking along these lines is that, in the genetic mutation that's protective, where you see kinetic stabilization of transthyretin by analogy, we also see kinetic stabilization of transthyretin with tafamidis over the dosing range of 20 milligrams once a day, from Cmin to Cmax.

So the assay that we use to -- the challenge with transthyretin in assessing its stabilization is that it's an unusual protein in that it's kinetically stable, meaning that the barrier is very high for assessing denatured states. Most proteins go back and forth very quickly. This protein does not.

So the destabilization assay that we use involves adding urea and then looking over two days at how much tetramer goes away as a consequence of dissociation and denaturation. That test was validated by amino turbidity and can be used in the clinic readily. And I think by analogy with the genetic mutations, and by analogy with the clinical data you saw today, would be a very good way to assess patient compliance, number one, and likelihood of clinical benefit, number two, from my perspective as a chemist. Okay?

DR. LOMBARDO: Dr. Grogan, would you like to come up and speak to TTR as related to our clinical program?

DR. GROGAN: Yes. Can I have the slide on change in NIS-LL by TTR stabilization status? So when we initiated this trial, we had this hypothesis, and we did not know what proportion of patients would demonstrate stabilization. So one of the analyses that we pre- specified -- can you please show us slide 130 -- is, at week 8, where we've already achieved steady-state plasma concentration, what happens -- let's look

at those patients who have a stabilized tetramer at week 8 versus those patients who are not stabilized at week 8.

What happens to their NIS-LL over time? And you can see on this graph here that in the upper red line, it's those patients who do not have stabilization of a tetramer. And in the lower green line is those patients who do have stabilization of their tetramer at week 8. And you see a statistically significant difference between the treatment groups.

Now, as it turns out, obviously, the vast majority of patients on tafamidis were stabilized and almost no patients on placebo, so this does match what we see in the treatment group response.

DR. FOUNTAIN: Did that sufficiently answer your question? Is there a follow-up to that?

DR. KATZ: No.

DR. FOUNTAIN: Dr. Preston?

DR. PRESTON: I had a question about the NIS-LL scale. In some of the analyses over time, it appears that, that was analyzed as a continuous variable, but that scoring is actually an ordinal rank.

So I want to know why the statistics were done that way, because obviously the proper statistics for an ordinal scale is different than a continuous scale.

DR. LOMBARDO: So Dr. Schwartz, could you come up and please discuss the analysis method?

DR. SCHWARTZ: My name is Jeff Schwartz. I'm a statistician at Pfizer. The analysis was performed on the NIS-LL change from baseline as a continuous variable. It's a combination of lots of subcomponents forming a numerical score. So analysis as a continuous variable is a reasonable method for analyzing that variable; used in MMRM analysis, which also takes into consideration the available data. So it adjusts, in a sense, for the missingness of the data as well.

DR. FOUNTAIN: Is that adequate? Is that an adequate answer for you?

DR. PRESTON: The problem I have here is that, obviously, the difference between, say, a score of 2 and 4 is different than a score of 10 to 12. You could have it many different ways. So I was just bothered when I saw that it was a continuous variable because the proper statistics are usually different for

that. I'm still not 100 percent sure why that was done.

I mean, obviously, when I see that, I'm concerned about, well, if the statistics were done for -- an ordinal scale may not have shown clinical significance, but when they're done for a continuous scale, they do. The continuous scale is not the proper statistics here.

DR. FOUNTAIN: So maybe we can discuss the properness of it when we discuss the other issues, but is there a specific response to that?

DR. LOMBARDO: Dr. Schwartz, do you want to come back to address that?

DR. SCHWARTZ: So I believe the range of values for the NIS-LL scale is 0 to 88, if I'm correct, so the variable has a possible range of 88 points. These patients are repeatedly measured over time. It seems like a reasonable way as to take into consideration that continuous value from 0 to 88 as a possible score.

DR. FOUNTAIN: Thank you.

Dr. Logigian?

DR. LOGIGIAN: I just had a couple of questions. But I wonder if someone can address the balance with respect to the severity of the NIS and the QOL scores in the dropouts. That is, do we know that the treatment group dropouts were, in terms of severity, about the same as the placebo group dropouts and that they weren't more severe?

DR. LOMBARDO: Dr. Grogan, could you come to address that, please?

DR. GROGAN: Yes. We did look specifically at the liver transplant patients who discontinued, as you recall, 13 in each treatment group. And when you look at the baseline demographics and disease characteristics of those patients who dropped out for discontinuation, two things are apparent.

One is, as a whole this group had longer disease duration and worse NIS-LL scores than those who did not drop out due to liver transplant. And we interpret this as being that patients have been on the liver transplant longer. They've been waiting longer for their organ and their name finally got called.

But when you look at those patients who did

drop out due to liver transplant across the treatment groups, their severities and disease durations were similar. There were 13 in each treatment group and, although they were more severe than the ones that did not drop out, the placebo patients looked similar to the tafamidis patients.

DR. LOGIGIAN: So are you saying there was no statistical difference or significant difference between the NIS scores in the treatment dropouts and the placebo dropouts?

DR. GROGAN: Correct.

DR. FOUNTAIN: Dr. Katz?

DR. KATZ: There are two things. One follow-up to that. You say they're similar. Do you have a slide of the actual scores? The other thing is, were all 26 transplanted patients on the transplant list prior to the study?

I mean, generally, patients are on the transplant list, but do we know for a fact that all 26 were actually awaiting it prior -- awaiting transplant prior to the study?

DR. GROGAN: Right. We know the vast

majority of patients were on the transplant list. I can't give you the exact numbers of the 26 patients who went to transplant, but the vast majority of them were. I can't tell you 100 percent that every single one of them were.

DR. KATZ: You can't tell us now? I mean, that information is not available. Is that correct?

DR. GROGAN: Right. Correct. Yes.

Could I have slide E273, please? So on this slide is the disease characteristics for subjects who underwent liver transplant. You see it's 13 subjects per treatment group. The NIS-LL mean is 15 for the tafamidis patients, 13.8 for the placebo patients, and similar scores, summated 7, summated 3, again, similarities in the scores between the groups.

DR. KATZ: Just to follow up, do you have on-study data for any of these patients --

DR. GROGAN: Yes. We do.

DR. KATZ: -- before they left?

DR. GROGAN: Right. Could I have slide E274, please? So the majority, 73 percent, of these patients had no data post-six months. And many of these

patients had no data after baseline. So the number of patients represented on the slide here is small, but you can see this is the change from baseline at six months in those subjects who discontinued due to liver transplant and obviously for those patients who had six months' data. And you can see it's the change from baseline across the various endpoints.

So there does not seem to be an apparent difference in the worsening of these patients at the six- month time point.

DR. LOMBARDO: And just to follow up on that in terms of the liver transplant, in Europe for patients with TTR-FAP, as Dr. Grogan had mentioned, they aren't assessed or moved up the list because of disease severity. Since they don't have liver disease, their assessment and placement on the list is due to time on the list, and they move up according to that. So she had mentioned that this was not salvage therapy, but their name had come up and they were called for transplant during the course of study.

DR. FOUNTAIN: Thank you. I'd like to remind the panel members, if you have a question, please raise

your hand. Follow-up or no? Okay, Dr. Chaudhry?

DR. CHAUDHRY: So the question is -- I guess you started by saying there are no prior directional trials for this disease. So I'm wondering whether there is any opportunity to look at the patients who did go for liver transplant and tell us what numbers they had;, if you did follow them out, those 26 patients, if there is a comparison.

I mean, is it, 100 percent of those patients get less than 2 point change in their NIS-LL versus the 45 percent, if you have similar 18-month data on the liver transplant patients, to give us an idea of what we're looking at; if there is a comparison, I mean, in the future perhaps, of a study between this drug and the folks who undergo liver transplant?

DR. LOMBARDO: Dr. Grogan?

DR. GROGAN: If I understand the first part of your question, you wonder if we have data on these endpoints post-liver transplant in those patients who underwent liver transplant. And then you questioned perhaps that might be a further investigation.

So of the 26 patients who discontinued, 5

died relatively immediately post-transplant, so they were not available to come back. We did request for the sites to have these patients return at least for a post- discontinuation follow-up visit. But many of these transplants were performed at sites other than the enrolling centers, so we have very limited data on the use of these endpoints or what happened to these patients with these specific endpoints.

But perhaps to address the question about what happens to patients post-transplant, Dr. Teresa Coelho, who again sees a majority of the patients in the world, could come up and give her clinical perspective about what happens to patients post-liver transplant on some of these neurologic measures.

DR. COELHO: As Dr. Grogan said, we have no regular assessment of patients that went to liver transplant because even if you call patients to come back, sometimes it's very difficult because they are being followed at transplant centers. But I think, in general, we can see that when we look at the results of liver transplant, we know that there is a very significant impact on the survival of these patients.

And we know that patients that receive liver transplant early in the course of their disease -- the majority of patients in the course of disease have a stabilization of the progression of disease for several years.

But we don't have from the literature much information about those patients that do progress and how much do patients progress after liver transplant. And from my clinical experience, I know there are patients that continue to progress after liver transplant without a significant effect of liver transplant, and there are patients that slow progression but continue to progress. And you have also patients that have a quite stable situation after liver transplant and those are the patients that receive liver transplant early in the course of the disease.

DR. FOUNTAIN: Thank you. We do want to move to have a break soon, so please limit your questions to clarifying questions because we'll have opportunities to discuss other specific questions later as well.

Next is Dr. Frank.

DR. FRANK: So how many patients in the U.S. were exposed to tafamidis? And I ask this

for two reasons, one from the agency perspective. Is there a precedence for approving a drug with very few U.S.

residents being exposed to a drug?

Also, the U.S. is not an endemic region and there may be genetic and clinical characteristics, differences in characteristics, that may have implications for the generalizability of the studies.

DR. LOMBARDO: So the patients from the U.S.

who were in the clinical program, were in the 1-A-201 program, I believe there were 10 U.S. patients in that study. The generalizability question that you get at, to speak to that, first it's important to recognize that although the U.S. is a non-endemic region with a number of different mutations, the V30M mutation is still the most common single mutation in the U.S.

patient population, representing approximately 40 percent of patients.

Then, as we think about the generalizability of tafamidis's effect for these patients, we do know that the underlying mechanism of TTR destabilization

actually occurs with all tested mutations, so all mutations that are known form these unstable tetramers, as Dr. Kelly had provided.

So in the 1-A-201 study, eight different mutations were enrolled. And then in addition to that, there was ex vivo data where a total of 36 mutations were tested with tafamidis and shown to be stabilized. So given the mechanism of action and the universal destabilization of tetramer, as represented in the V30M mutation with the clinical effect, we believe these results are generalizable to the U.S. patients.

DR. FOUNTAIN: All right. Dr. Farkas?

DR. KATZ: Just let me quickly answer part of Dr. Frank's question, which had to do with the precedent for approving a drug with very few patients in the U.S. There's certainly precedent for approving drugs where there may be no U.S. patients. But of course, we have to be confident that the data that were generated, wherever they were generated, are applicable to the U.S.

population. And here, we've heard that there's sort of a general sense, I think, being

described that, once you have stabilization, you're going to respond the same regardless of your geographic location or independent of your mutation. I think that probably remains to be seen.

But to answer the simple question of, is there precedent for approving drugs with few to no U.S.

patients, the answer is yes, assuming we can conclude that the patient studied were like the patients in the U.S. and that patients in the U.S. will respond similarly. And there are a lot of things that go into trying to answer that question.

I had a question. You can decide if this is a clarifying question. We can deal with it this afternoon. That's fine with me. But a lot of the data presented were open-label, unblinded data. So in those, particularly Study 006, settings we always are concerned about outcomes and knowledge of treatment assignment, particularly outcomes that are highly subjective, whether a patient is assessing them, or a clinician, or a caregiver. But some of the outcomes are asserted to be objective. And of course, those are the sorts of things we're interested in, in open-label

settings because presumably they're not susceptible to blind breaking. Specifically, there were the sum 7 and the sum 3.

So my question is, can we get a detailed description of the components that go into those measures, and are they truly objectively rated? Could we get a machine printout or does someone have to look at the output? And again, there are many components to these things and we can deal with that this afternoon, and whether or not those are susceptible to knowledge of treatment assignment.

DR. FOUNTAIN: Perhaps that might take a few minutes to get that slide together, so maybe this would be an opportune time to take a break for a few minutes and then come back after the break and answer the question. That might give you an opportunity to get those specific things together.

The specific question, if I can reiterate, is what are the subcomponents of the sigma 3 and the sigma 7, and exactly how are they measured, so we can make an assessment about how objective they are.

DR. KATZ: And how susceptible they are to

knowledge of treatment assignment by the assessor?

DR. FOUNTAIN: So we'll now take a 10-minute break. Panel members, please remember that there should be no discussion of the meeting during the break amongst yourselves or with any member of the audience. So we'll resume in 10 minutes at 11:13.

(Whereupon, a recess was taken.)

DR. FOUNTAIN: All right. Please take your seats.

All right. If we can resume the panel discussion. Before the break, the question at hand that Dr. Katz asked was, what are the specific subcomponents of the sigma 3 and sigma 7 that might be objective, or are there other objective measures that might be less influenced by knowledge of being on the treatment?

DR. LOMBARDO: So to speak about the objectivity specifically of the measures that were used, certainly I think that the mBMI and the TTR stabilization are very objective measures that were used both in 005 and 006.

Then more globally, just to note, as patients

entered into 006, in all their measures, both patients and physicians were blinded to the treatment that they had been on 005. Certainly, as we're looking across the group and the changes in slope between the placebo-tafamidis patients and then the tafamidis-tafamidis patients, that maintains the indication that the blind was maintained.

But specifically to speak to your question about the sum 3 and sum 7, I'm going to have Dr. Freeman come to talk to the components of those composites.

DR. FREEMAN: So if I could have the slide on the sigma 7 and sigma 3 on the screen. While we're waiting, the sigma 7 you will recall is the predominantly large fiber measure and the sigma 3 is a small fiber measure. The sigma 7 comprises standard measures of nerve conduction. The peroneal nerve, tibial nerve, and sural nerve, these are the major motor nerves tested by any clinical neurophysiologist in the lower extremity.

These are totally objective tests. So there is an electrical stimulus. There is a response. If

done by somebody trained, this will be an objective test, no patient response, no patient involvement at all.

Continuing on the left side, we have quantitative sensory testing. Over here, there is patient involvement. This is a graded, quantified sensory test in which there is a stimulus and the patient interprets the stimulus. There is the potential for there to be some patient bias in the testing, but it would be hard for the patient to even know which direction to respond.

But this is a psychophysical test, and there is some potential for subjectivity. The heart rate variability components, for statistical reasons, in the development of the test of the large fiber battery and in autonomic tests, therefore, a component of the small fiber battery, is again an objective test. There is a stimulus, deep respiration, and a response, the heart rate response, an objective measure.

So in answer to the question, predominantly and in large part, an objective measure of neurophysiological function.

DR. FOUNTAIN: Is there a follow-up question to that or a separate question?

DR. JILLAPALLI: While I agree that nerve conduction studies are quite objective, it's also true that knowledge of unblinding can lead to all sorts of manipulation by the operator in terms of the amplitude, in terms of the voltage, the current delivered, and the placement of the electrode. And there are experts here who can speak to that. So it's not entirely as objective as it might appear.

DR. LOMBARDO: If I may actually ask Dr. Grogan to come up, because she can speak to specifically the measures that were put into place as we were conducting both 005 and 006 with regard to potential unblinding.

DR. GROGAN: All of the investigators at the sites were trained at an investigator meeting and they were qualified for the performance of these various physiologic measures by an independent neurologist prior to them enrolling any patients into the 005 study. So these same investigators and neurophysiologists followed patients from 005 into the

006. The prior blind in 005 was maintained, but the sites were aware that this was an open-label trial, with all patients on tafamidis.

DR. FOUNTAIN: All right. I think Dr. Farkas was next.

Did that answer the question? But before your presentation, did you have a question?

We have one or two more questions before your presentation, one from Dr. Clancy, if you still wish to ask it, if it's a clarifying question. This was a discussion question.

DR. CLANCY: This is a clarifying question.

So I appreciated the talk that Dr. Coelho gave from Porto in Portugal. And I guess my question is, among these endemic centers, where the population itself must be aware of this disorder because they've got an uncle or grandfather with it and the doctors who have seen many, many cases of this, were the systematic differences in the patient status among all the endemic centers that enrolled patients versus just the one in Porto, Portugal?

DR. LOMBARDO: So I'm not sure if I

understand the question. Were you asking if there were differences in the patient populations across the sites?

DR. CLANCY: Yes. At enrollment, in terms of the severity of disability, were they detected earlier in a milder state in these endemic places?

DR. LOMBARDO: I understand.

Actually, Dr. Grogan, did you want to come and maybe speak to the baseline characteristics of the patients in Porto compared to the others?

DR. GROGAN: The only other major endemic center that was participating in this trial was Sweden. The patients in Sweden, although it is a major endemic center with the V30M mutation, it's known in the literature that these patients tend to be older at the age of onset. But there actually was a publication that looked at, regardless of the age of onset between these sort of late onset patients versus early onset patients, that once neuropathy has been established, the progression is similar.

I don't have the baseline demographics of Porto versus Sweden, but I can tell you that the

Swedish patients were definitely an older population.

DR. FOUNTAIN: Thank you. The last question before we move onto the FDA presentation will be from Dr. Gooch.

DR. GOOCH: I have a couple of clarifying questions. The first is, in the 005 study, the secondary endpoint analyses that shows statistical significance, were those based upon the efficacy evaluable population or were they intent-to-treat? Were they all at 18 months versus baseline? Could you comment on that?

DR. LOMBARDO: Actually, Dr. Grogan, could you come up and maybe take us through the different analyses from the co-primaries?

DR. GROGAN: All the change from baseline analyses that we showed up here were in the intent-to-treat population. You're just utilizing a mixed model repeated measures analysis.

DR. GOOCH: Thank you. The second question I have has to do with the 201 study. Have you accumulated enough patients there to do variants versus baseline analyses and compare with historical controls

to come up with significance, or have you had any analysis of that kind on that study?

DR. GROGAN: Right. I mean, it's a relatively small study. Eighteen patients completed the trial across eight different variants, so it's really hard to look at a by-variant progression. So I'm not sure I can adequately answer that question.

DR. GOOCH: The third question I have is, in the 303 study, do you have any data beyond 36 months regarding continued benefits, potential benefits of the medication with the statistical analysis?

DR. LOMBARDO: So the 303 study, as we mentioned, is a continuation study, and patients remain in that study. And some patients have been in for up to five years. The data from those studies were not included in this NDA. However, we continually analyze those data and can say that -- very top line, if I may, with permission -- that the data are consistent in terms of the continued rate of stabilization.

It might be helpful, actually, if -- Dr. Watsky would you like to come up and comment on 303, please?

DR. WATSKY: Hi. Eric Watsky. I'm a physician at Pfizer. And yes. The 1-A-303 study has data out at this point to 42 weeks. This data, however, was not for efficacy -- or this data was not included in the submission. So without permission, we would not be presenting that. But as Dr. Lombardo indicated, the results are consistent. What we're seeing in terms of response rates is consistent. More than half of patients remain responders in the population that are studied out to 42 weeks.

DR. FOUNTAIN: The sponsor will be here all today, so you'll have opportunities to ask more questions of them later if it's particularly for discussion questions that aren't so clarifying. And we want to be sure to be fair to give the FDA an opportunity at their presentation as well.

So it's 11:26 now. Dr. Farkas will present the FDA presentation. And we'll delay lunch until 12:15, but we do have to resume at 1:00.

Dr. Farkas, will that give you sufficient time, or would you like to divide your presentation between before and after lunch?

DR. FARKAS: Sorry. I didn't actually hear what the time --

DR. FOUNTAIN: Would you like to divide your presentation?

DR. FARKAS: I didn't hear what the time was, though.

DR. FOUNTAIN: So it's 11:27 now, 11:30, and we should probably break for lunch at 12:15 in 45 minutes.

DR. FARKAS: I think that's okay, and then maybe the clarifying questions can be after.

DR. FOUNTAIN: The clarifying questions after. That would be perfect.

DR. FARKAS: I think actually that Dr. Katz covered a fair number of the things that are in some of the slides.

DR. FOUNTAIN: You just take your time to do whatever you think is necessary just in terms of timing.

DR. FARKAS: Sure. Thank you.

So I think the panel would have noticed that there really isn't any discussion of safety in these

slides. It really focuses on efficacy, but of course, we can discuss safety this afternoon.

As Dr. Katz had said this morning, to be approved, orphan drugs, like any drug, needs substantial evidence of efficacy. That's usually two positive studies or one very persuasive study plus confirmatory evidence. There is one controlled trial for tafamidis. And the FDA is committed to applying flexibility in trying to figure out how the data from that trial fits into the evidence that would be necessary to support approval.

Dr. Katz also mentioned some characteristics of a particularly convincing study. And I won't go over all of them. But I think what I'll concentrate on is the part about serious weaknesses. I guess what happens is that if there are, for example, baseline imbalances, baseline imbalances can arise by chance. And then the study arms can be different, truly different, but by chance -- and some of my later slides will talk about that. Then if different endpoints are used to measure differences between the arms, the different endpoints are very consistent. They're

measuring this difference that arose by chance.

So that's one important reason that, for approval based on one study, there have to be no serious weaknesses.

Again, this red box mentions post hoc changes in analysis, a clear prior hypothesis. And so I'll also stress it a little bit later, but to mention here, when we take a look at the data, as is usual in science, we take a look at the primary endpoint. And that is the most reliable endpoint.

So the co-primary endpoint in Study 005 was the NIS-LL and the Norfolk. And so, as a co-primary, the study is positive only if the p value for both is less than 0.5. The reason for having co-primary endpoints is that small changes in NIS-LL -- it's a physician exam -- might not represent benefit that the patient perceives. The Norfolk is combined with that because that's measuring what the patient perceives, to see if the change has a clinical impact.

Now, the p value is shown separately for the NIS-LL and the Norfolk. And on the primary analysis, it has been said it's .07 for the NIS-LL and .12 for

the Norfolk. And I should say that's commonly thought of as negative. I mean, actually, that's I think problematic terminology, and it's a little difficult to go into. I won't. My boss is winking at me or something.

(Laughter.)

DR. FARKAS: But I think that we should keep in mind that .05 doesn't mean efficacy proven and .06 means efficacy absent or certainly not efficacy disproven. So one interesting thing about taking a look at co-primary endpoints is that we kind of automatically do look at .07 separate from .12, which brings up this problem of multiplicity.

So if we were looking at these two separate endpoints, we would have thought the p values for efficacy should be .025, so just doing that kind of typical correction if we're looking at two different endpoints.

And I think we've already done that. I mean, when we got this application, we certainly did, I mean, in the review division. And so that starts bringing up the issue of multiplicity, that we've in a sense

already looked at three endpoints, looking at this one slide.

In this slide, it just says that again. It says that when we consider multiple endpoints, there is an increased risk that we conclude the drug is effective when it isn't. And I said here that it's in ways that cannot be quantified, but it's a large effect -- and I guess maybe it should have been bolded -- if we keep looking at enough endpoints, we're guaranteed to find endpoints that are positive. That's what a p value really means. And that makes the study no longer adequate and well-controlled, and not capable of providing reliable evidence.

There's a caveat to that. And that is, we don't only look at the statistics. If there's a really big difference, that might be true, and we've talked about the TTR stabilization. I think it's not clear to the division what that means. But when there's a really big difference, then we're not so stuck by the multiplicity problem that we would ignore that.

So this is a sensitivity analysis on the efficacy evaluable population, and we've talked about

that. And this can be helpful, again, with caveats, multiple testing, perhaps biases. It can be helpful for understanding the data. It really doesn't replace the primary endpoint. I think that really does need to be stressed. But it can help in interpreting the primary endpoint.

Then there's this question of baseline imbalances. I'll spend a couple of slides talking about that.

So it's reasonable in the previous slide to explore the robustness of the data by taking a look at the efficacy evaluable population, and that led to a lower p value. And then this slide is a sensitivity analysis considering baseline disease severity.

Certainly, when the study was being planned, it was realized that, that might be an important covariate. And while it wasn't included in the primary analysis, it was pre-specified. Again, pre-specified doesn't mean there was an order of analysis, so we've tried to keep that distinct. But it's a pre-specified analysis, and a reasonable analysis, and an important analysis because one could worry that baseline disease

severity would affect how patients progressed.

So by that analysis -- and I should say, there are different ways to do this analysis. But by the analysis done by the FDA statistician, which is a typical way to do it, the p value is .16. So we start collecting a number of p values, some greater than the primary pre- specified analysis and some less.

Then to explain a little bit more about what might happen in a study by chance and how we might separate that from what might happen from a drug effect, the NIS-LL, in the tafamidis arm, was 2 points less severe. You should keep that number in mind. And that was despite 12-month longer symptom duration.

So we would think -- we don't know, but we might think -- that knowing what we do about the disease, that if patients had the disease for 12 months longer, they should have a more severe NIS-LL score.

So putting those two imbalances together, it makes one concerned that, despite randomization and purely by chance, the prognosis of patients in the tafamidis arm was better than the prognosis in the placebo arm. And the p value of that difference

actually says something interesting. It can't be stressed enough. It does not mean that the imbalance was important. What reasonable interpretation is, is that this kind of imbalance happens in a lot of studies, which could be seen as one reason that a single study is less reliable than two studies showing similar findings. These kinds of imbalances can be important and they occur not uncommonly.

So to try to understand the implication of an imbalance, we have to look at the size in the implications and how it fits with our understanding of the disease.

So getting back to the size of the imbalance, so the top shows a 2-point difference in severity. That's the imbalance. And then the bottom shows a 2.5 difference between the arms at 18 months. There's no disagreement that the top 2 points arose by chance.

I think one has to be concerned that when one sees the two point differences arise by chance -- at the end of the study, a 2.5-point difference might have arisen by chance -- which is really what the p value is telling us for the primary endpoint to begin with. We

don't know that it occurred by chance, but there's certainly that concern.

The concern had been expressed before about most of the patients coming from a single site in Portugal. Perhaps this has already been covered, but there certainly is reason to be concerned in FAP that there are differences that we do not understand in the course of the disease in Portugal versus in the United States.

I think it's already been mentioned, but just to stress, the penetrance is very different with the same gene mutation, V30M. Penetrance is very different. It's related to age of onset, but age of onset is very different, different by something like 20 years. And that number is actually from France, but I didn't come across numbers for the United States, but in endemic regions versus non-endemic regions.

In this particular disease, that might give increased reason to be concerned that there could be differences in the way the disease acts, the way the drug might act in one site versus another.

Probably a stronger worry that the division

has is the one about evidence of efficacy from more than one site. And it really does go to the heart of internal replication. What does internal replication mean?

In our guidance document on efficacy, there's a quote here, that, "If analysis shows that a single site is largely responsible for the effect, the credibility of a multi-center study is diminished." So that's certainly something that we worry about.

Now, the secondary endpoints, I'll talk about, but just to remind you, we have a problem with multiplicity, and we have to consider that. And so we've already looked at the co-primary endpoint, the individual endpoints, the efficacy evaluable endpoints.

So even before we start looking at the secondary endpoints, we know there is multiplicity that needs to be accounted for. And then the secondary endpoints did not have a pre-specified order of analysis, which was mentioned before, and that compounds the problem. And really, the secondary endpoints don't represent an adequate and well-controlled trial. And the statistical significance

doesn't apply to nominal p values. And the reason is that small p values happen by chance, and perhaps not extremely, extremely small p values. That was maybe what comes up with the stabilization assay. But pretty small p values occur by chance when one looks at a lot of endpoints.

Now, the large nerve fiber secondary endpoint had a p value of .06, which by usual accounting would be considered negative. And the small nerve fiber function had a p value of .005. I think it had been brought up before -- well, actually it was a different point that had been brought up. But those two endpoints actually aren't really consistent with each other. And then when one looks at the small fiber endpoint, a .005 p value was seen in Study 005. And then in the continuation, circled in red, it looked like the endpoint worsened. It looked like the patients got worse.

I wrote "worsened" there, too, actually, but it just looks like that, maybe. I mean, you don't know. I guess that's the point. You don't know. But taking a look at the error bars, maybe the more likely

explanation is that that's what experimental noise looks like, that the .005 p value occurred due to experimental noise. And it was one of many endpoints tested. One was caught when it was a small p value. And then the next time one looked, it wasn't such a small p value, and that's to be expected.

Now, the modified body mass index is an interesting endpoint, because if you just take a look at body mass index, it actually helps to illustrate problems with biomarkers. So the body mass index in this disease is not a good measure of nutritional status without the modified part because, when albumin goes down, edema can go up, and you can get the false impression that the patient is gaining weight when they're doing worse. They're just gaining water.

Now, BMI ought to, all other things being equal, correlate with your weight, nutritional status, or whatnot. But we can see already that it doesn't really work unless you account for other factors. And that here is edema.

But the concern would be that you know this measure is susceptible to problems, to not predicting

the clinical outcome. But do you know in all the ways that, that could happen?

So the pattern of change in, again, the p values, it does look like, even despite multiplicity, something maybe did happen with the modified BMI. The meaning of that isn't clear to us. That's a question.

If you first take a look at the pattern, there's an increase in mBMI in treated patients in Study 005, but that doesn't really seem to keep increasing. So if there was some continued benefit, some continued increase in nutritional status, one might think that that would keep increasing in Study 006.

There are other things, too, one might be worried about. The increase happens very quickly, so I'm not sure if there was any measures before month 6, but at month 6, there was an increase, and then it seemed, as far as we could tell, to be stable.

So it might be some kind of -- I don't know the right word -- maybe biochemical effect. And we had written down, "Well, many drugs can change weight without changing nutritional status." You can think of

the simplest maybe being salt. So that's a concern.

Just going back to the pattern, too, when the placebo patients were switched to drug in Study 006, there was a rapid increase in the mBMI. And there was an analysis in Study 006 about an early start effect, where you could try to show that the drug worked because, after you started all patients on drug, they would stay separate from each other, that there would have been an advantage to treating patients early.

So here, it doesn't look to the division perhaps like this would support that.

Then there are other really more technical questions about what this assay is showing, what effects it's sensitive to. So the TTR binds to albumin. Sorry. The tafamidis binds to albumin. And there are concerns that the division has that this could change the accuracy of the test, so a purely analytical issue. But then maybe there is some change in the amount of the albumin. Tafamidis binds to albumin. Tafamidis binds to TTR. We think we see -- it wasn't really talked about -- an increase in the amount of circulating TTR. But I don't think there's

any thought that that contributes to efficacy.

So tafamidis increases circulating TTR. It doesn't seem to be connected to efficacy. Tafamidis increases, perhaps, circulating albumin. And it isn't clear that that would be associated with efficacy.

So looking at the open-label study 006, it's been mentioned that this is not adequate and well-controlled. But still, we pose the question, could this provide confirmatory evidence?

Some of these points were raised about open label, concerns about unblinding. But there's some other points worth mentioning. Many endpoints were tested, but that is a multiplicity problem.

But when one looks at effects in Study 006, it's not independent confirmation there were effects from Study 005. And I think we have to be cautious in double- counting, as you might say, effects that occurred in 005 as having occurred in 006, so when an analysis is done over 30 months, where is that difference coming from?

Now, the division took a look at the pattern of change in endpoints in Study 006. And I picked a

couple because they're kind of opposite. So the one on the bottom, the small nerve fiber I had shown before with that red circle around it.

Now, there's kind of two possibilities about what happened to the small nerve fiber endpoint in patients who started on tafamidis and continued on tafamidis. Maybe they got worse. As I said before, maybe that is just an expected pattern of experimental noise.

With the change in Norfolk, there was some discussion before. I mean, the division has some concern about unblinding and subjective endpoints, but just kind of looking at the size of the differences, one might worry that, that fits into size of change that can happen by chance, too.

Now, I should say, this is a little bit more complicated, but one has to think about what pattern of disease progression and really what pattern of endpoint progression one might expect.

So with the small nerve fiber endpoint, a within-arm comparison was done, and actually for the Norfolk, too. So the slow untreated was worsening more

rapidly than the slow after treatment began. And so there's a thought that maybe the slope decreased because of treatment. But this is a problematic analysis with this kind of data, this kind of endpoint.

So the rate of change of the endpoint may change with progression of the disease in untreated patients. So this is from the observational study, FX1-A-001.

So I should say, too, that this is cross-sectional, not longitudinal data, so it is open to some kinds of biases itself, but the pattern is really concerning. And it shows that, seemingly, either the endpoint is less sensitive to change as time goes by, or maybe perhaps the progression of the disease changes. You can't really tell.

But when you go back, and you look, and you think about change over time in patients who went from placebo to tafamidis, what would need to be calculated in would be the change in the endpoint, how the endpoint responds. But that's extremely difficult to do. I mean, we really can't do that. We don't have the data that we need. And then some endpoints -- this

is the large nerve studies -- seem -- and again, this is cross-sectional data, so it could be open to some problems with this interpretation. But it certainly suggest that you could see something that looked like stabilization in this part of the curve because the endpoint isn't measuring change anymore.

These analyses of efficacy are based on change, but once something isn't changing anymore, say nerves in the leg, once those aren't functioning, they don't get any worse. So that introduces a great deal of complexity -- well, it makes it more than complex. It makes it unreliable to try to interpret what's going on with these open-label endpoints, which brings up the question of a path to approval. And this is just repeating from the first slide, that top bullet, and the second slide, too, Dr. Katz had gone over that, for subpart H approval, we need substantial evidence for an endpoint that's not actually the clinical endpoint of interest.

This just kind of shows graphically, diagrammatically, the confusion that often arises. So maybe it's worth looking at just one last time, that

what we need for subpart H is high confidence that the surrogate changed and reasonably likely that it predicts clinical benefit. But subpart H does not apply if it's reasonably likely that an endpoint changed, be it a biomarker or a clinical endpoint, even if there is high confidence that that change would predict clinical benefit.

So it's worth noting pathways that we don't have available to us in the United States, and, of course, tafamidis is approved in Europe.

In the exceptional circumstances -- I'm no expert in explaining this, but I copied this from the European site -- is that comprehensive data cannot be provided based on several factors. There is yearly review of new information, but normally, that will not lead to completion of a full dossier, or normal marketing authority, or authorization for the drug.

That's quite different from the pathway that we have available through subpart H, for which again we need substantial evidence. We did the post-approval study and that must show efficacy for the drug to stay on the market.

So the division considered -- with all the caveats about, worries about, the integrity of the study, the vision considered if there were endpoints that could support subpart H approval.

So the large nerve fiber function might be or if it was reasonably likely to predict clinical benefit. The p value was .06, again, normally considered negative. And then there are the other weaknesses and multiple testing.

The small fiber function, more or less, I've gone over before, that with multiple testing, it's not clear what the .005 means. And then there's other behavior of the endpoint that we're able to see in Study 006 that makes one worry about random variation, that would fit with the kind of effects that we see with multiple testing.

The NIS-LL could be considered a surrogate endpoint because, again, small changes might not be perceived by the patient, but using NIS-LL, again, goes back to, is there substantial evidence supporting that.

Now, the TTR stabilization assay has been perhaps maybe a little bit of confusion about what the

-- used in the study was actually testing. And maybe we'll have to discuss this later this afternoon.

But it does seem clear that non-physiological conditions were used to measure tafamidis stability in the clinical studies, and that that assay gives a measure of stabilization that is something like, instead of 100 percent or almost 100 percent, something more like two times slower dissociation or three times slower. There was some conversation about, maybe that assay is really taking the place of some other assay that would have been better. But perhaps that's part of the confusion.

I think that with the division's current understanding, it still seems to us that even under more physiological conditions, looking at other papers that were published, that dissociation still occurred at a much slower rate, but we'd probably be best to talk about it this afternoon.

So then there's just the stabilization and the idea of reasonably likely. And I think Dr. Katz had mentioned that we really need to understand the biomarker well, and we really need to understand the

disease well. And there are some particular characteristics of FAP that seemed very mysterious, like the difference in penetrance, and age of onset, and clinical course that one sees in different regions even though there's the same mutation.

So the division looked at the inherited protection by the T119M variant, too. But it isn't clear to us how comparable this kind of genetic therapy, if you will, form conception is to treating active disease. I mean, certainly, not only is an ounce of prevention worth a pound of cure, but some treatments that are preventative clearly don't do anything to treat an active disease.

Finally, of course, there's countless examples, as was mentioned before, of assays not predicting clinical benefit. And then maybe it's helpful to take a look at where we are with stabilization versus where we'd like to be with clinical symptoms.

I think, normally, the way the FDA thinks about endpoints reasonably likely to predict clinical benefit is effects that have changed. Here, it's

actually changes that are at the organ level or even at the level of clinical signs. It doesn't mean that we can only think that way; we just usually do. But even before that, there's questions about something happening at the cell level or at the tissue level, and even what's going on with intermediates in the blood of patients.

So we're really at the very earliest part, something going on in a test tube, but we don't know. We know almost nothing about what's going on in the patient. So then there's some ideas about a path to approval if more data is necessary. And let me first say that the everybody in the division knows that saying another study might be necessary means a lot of difficulty. Ad I think we really tried to think of everything before we bring up another study. But once we do bring up the idea of another study, we really try to figure out how it can be done.

So V30M patients -- which there are not a lot; we understand that. One thing, though, is that perhaps the knowledge from Study 005 might make it possible to do a better study if another clinical study

was done. There are also patients from other endemic regions, or there are not a lot of patients, but it's a consideration there are patients.

Non-V30M patients, there's a hundred different mutations. If all those patients respond the same way to the drug, those patients could all be studied, essentially just like the V30M patients. There's also pre-symptomatic patients, which is an interesting idea because there's no data available for those patients. And yet, seemingly, with a treatment like this, the first thing that you might think of is, should we intervene earlier.

So that's definitely data that we would like to have and, in a way, a new population or additional population that could be studied.

Then familial amyloid cardiomyopathy was mentioned before, and that is a closely related TTR amyloid disease. And efficacy for FAP can be supported by efficacy data from FAC if we decide that the two diseases are similar enough. But that seems to be the argument that's being made. We could discuss that, but it seems perhaps reasonable. There's also age-related

TTR amyloid cardiomyopathy, which is not a mutant TTR, but a wild type that causes an amyloid disease.

Now, these diseases are certainly under-diagnosed, and I don't think that there's tens of thousands of patients today diagnosed in the United States with these conditions, but they're almost surely there. So for example, 3 percent of the African-American population carries a mutation that causes familial amyloid cardiomyopathy.

As far as options for study design, A just shows normal accrual of unexposed patients, but the FDA is flexible about study designs. And the randomized withdrawal design has the benefit that patients have already been identified, minimizes the accrual time, and patients can be withdrawn from the drug. And I know that that's a concern.

But if done carefully, a very, very small amount of change can be identified in patients. I think that's the key. Nobody has the intention of putting patients on placebo for years at a time and doing nothing as they get worse. But through careful study design, that kind of concern can be addressed.

There's some other options here, like high or low dose, or low-dose response. And I think it gets back to the efficacy that was seen from the 20 milligrams, in that while there's perhaps a sound theoretical reason to say that the drug doesn't get any better than this, it certainly seems like there's reasons to try to look, to see if the drug can do any better than this.

The adaptive design comes in because we think that there is ways that those response studies can be done. And while there's the concern that it takes too many patients, we can try to enhance efficiency of such studies through adaptive design.

This is the last slide. The box really points out two things that we need, that the patients need. They need evidence that drugs are effective, and they need a minimal wait time for an effective treatment. It really needs to be effective.

It was brought up before that there are actually options that there are actually options that could be discussed about expanded access, that is giving tafamidis to some patients while other patients

are being studied. And in TTR diseases, there are some seemingly natural populations that one might treat and that one might study. So there are FAP patients with the polyneuropathy and there's FAC patients with the cardiomyopathy. And we don't have any information available about efficacy in the cardiomyopathy patients right now.

So one might think about allowing patients with FAP to be treated with the drug while patients with the cardiomyopathy were being studied. And then the cardiomyopathy data, if the study was positive, would very much support efficacy in the polyneuropathy patients.

There's other possibilities, too, so I had mentioned before there is a study that's been done on symptomatic patients with FAP, but not on pre-symptomatic patients, so it would be possible to treat symptomatic patients, but tend to have a study with pre-symptomatic patients. Anyways, there are different ways it might be structured. And, of course, one advantage of this is that we kind of minimize the wait for drug and seemingly maximize our ability to show

that the drug is effective. Thank you.

DR. FOUNTAIN: Thank you. I think we have time for some clarifying questions now, if we could delay lunch for a few minutes, so let's start with Dr. Preston.

DR. PRESTON: I have a very important question. I think that if both of the primary outcomes had shown statistical significance, this proceeding today would be very easy, at least for me.

So my question has to do with the intention to treat versus the efficacy evaluable. Intention to treat is obviously extremely important to keep the power of randomization.

However, I'm concerned that this particular study is quite unusual because the people who dropped out, they dropped out because of liver transplantation. When I think about people leaving a study, I think about, maybe they decided to move, or they decide to quit, or there's a side effect of treatment, or they decide they want to stop a treatment and do another treatment.

But in the case of liver transplant, the

patient is given this one opportunity, which they have to jump at. So here we are. I have this disease that has no cure. And here, a liver is available for me, and no one's not going to jump at it.

So the question is, normally, I would really stick to the intention-to-treat analysis no matter what, but the question for you is that, is this a time where the efficacy evaluable analysis may actually be more apropos?

DR. FARKAS: I think that would be a great question for discussion, and I'm not going to go there right now. But I think we should talk about that this afternoon. I mean, I would say, I guess, that I think there were some concerns that I outlined with other aspects of the study. I understand the question, but maybe we can postpone that.

DR. FOUNTAIN: That would be great.

Dr. Shefner?

DR. SHEFNER: This would be more of a clarifying question for me because, in your presentation, it leaves me confused. It seems like you're proposing potentially contradictory pathways.

At the beginning, you very clearly laid out what the criteria are for approval, either under part H or under normal regulatory approval. And then in your last two slides, you proposed ways where the drug could be made available and studied in other populations.

It seems to me that those potentially are inconsistent. If we're being given a clear set of guidelines, which are actually legally mandated, then are we then being encouraged to ignore those and encourage other ways to make the drug available?

DR. FARKAS: Yes. I think I didn't clarify, and it's really important to clarify that during the development stage, prior to approval, there are regulations that allow treatment of patients, therapeutic treatment under an IND. So it's prior to FDA approval. It would be prior to any kind of approval, subpart H approval, full approval. So it comes up in situations where you are conducting the studies, you can still successfully conduct the studies if you have patients available to do that, to find the evidence you need.

Then there are patients who aren't in the

study for one reason or another. And if you can decide that treating those patients won't interfere with the gathering of necessary efficacy data, that can be done under the regulations.

DR. SHEFNER: The second part of my question about clarity is that, in some ways in your presentation, you seem to be using nominal p value strength to gauge how seriously to take a given result.

You pointed out one set of inconsistencies, which are that the small fiber subscore seemed to reach a higher level of significance than the large fiber subscore. I just wanted to point out that there is one higher level of inconsistency, which is that the NIS-LL is primarily driven by strength, which is a purely large fiber phenomenon.

So it seems to me that the primary outcome, which is a large fiber score, shows potentially significance. The subsequent secondary outcomes are inconsistent in that the large fiber sum score is less dramatically significant than small fiber.

DR. FARKAS: Right. Thanks for pointing that out. Yes. We're concerned about that.

DR. FOUNTAIN: Just to clarify your first question, was your first question actually, is it possible to approve the drug given the statements made?

DR. SHEFNER: No. I think my question was, how should we guide our discussion? I mean, if in fact we conclude, based on the instructions of how drugs are approved, that this is not a study that allows approval, how is it intellectually logical to go forward basically by approving a plan that allows not just an IND-level access, but expanded access to everyone with this disease while studying an entirely separate disease.

DR. FOUNTAIN: I just want to clarify that, if that is your question, it got answered adequately.

DR. FARKAS: I think it didn't probably, but I think Dr. Katz can take another shot at it.

DR. KATZ: Yes. The rules are the rules. They're flexible, as you've heard. But they have to follow -- one or another of the standards, for example, showing effectiveness, has to be demonstrated whether it's a clinical, or a lab, or a surrogate.

But I think what Ron was presenting was sort

of various options. We're saying, if we're thinking about subpart H, the surrogate approval, accelerated approval, let's look at what are the potential surrogates and what are the problems with those data.

If we think that you can't get to subpart H and it can't be approved, here's a way to make the drug available to some patients while it's still being evaluated. So I think those were just different options that we could possibly go with.

DR. FOUNTAIN: Dr. Cohen? Dr. Kramer?

DR. KRAMER: Yes. Maybe the agency could clarify. There's a guidance on compassionate use or that equivalence. What kinds of efficacy criteria are usually implied by allowing compassionate use?

DR. FARKAS: Let me think. I don't have a slide with that, but the expanded access regulations were recently updated, whenever, a year or two ago. And I believe it was with the intention of allowing more use of drugs by patients who were not being studied, while studies that were capable of showing efficacy were ongoing.

So there's a paragraph that describes the

kind of evidence that you would need to start an expanded access protocol. And it's, I think, fairly liberal and we could, of course, look it up at lunch. But it says something like, there's one positive study, or one study that leans, or something else that makes you think the drug might be effective. And so it really goes down to the level of using judgment.

DR. KATZ: But they aren't approval regulations. They're ways to make a drug that is still investigational, that is not approved, that is being evaluated to ultimately perhaps be approved, to make it available to a wider group of people. It's not a way to make it more available attached to an approval.

DR. KRAMER: Just to clarify, my reason for asking that is, there still has to be some level of evidence that the drug might work and so by recommending that, you have to have some thought along that line.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: I have a clarifying question for Dr. Farkas. On your slide 7, you look at the outcome adjusted for the baseline characteristics of the

patients.

DR. FARKAS: Right.

DR. CLANCY: My question is, was this calculation performed on the intention to treat or the efficacy evaluable population?

DR. FARKAS: I think this was on the ITT population. Yes. And Dr. Luan is nodding yes.

DR. CLANCY: Was there a calculation on the efficacy evaluable one?

DR. FARKAS: I'm just looking at Dr. Luan.

DR. LUAN: No. The p value is based on ITT population and the p value under the efficacy evaluable population, I did not perform.

DR. CLANCY: That might be worth knowing if that's one of your concerns. And we're going to have a later discussion about what is the appropriate population to include in our analysis. It might be worth knowing that.

DR. FARKAS: Sure.

DR. FOUNTAIN: Thank you. Dr. Chaudhry?

DR. CHAUDHRY: The same question Dr. Clancy had.

DR. FOUNTAIN: Dr. Frank?

DR. FRANK: I just wanted to clarify something that you had said regarding the co-primary endpoints. When we're looking at co-primary endpoints, does the total p value need to be less than .05 for it to be considered positive or each of the individual co-primary endpoints?

DR. FARKAS: It's each of the individual endpoints, so both less than .05, both at the same time less than .05.

DR. FOUNTAIN: Thank you. Maybe we could take the remainder of the questions after lunch just so we don't get so far behind.

DR. FARKAS: I shouldn't interrupt. I shouldn't interrupt you, I suppose, but Dr. Unger had something to say. And when he has something to say, I think I need to listen.

DR. UNGER: I just want to clarify one thing about that because it may not have been clear to everyone in the room. But Dr. Farkas was talking about multiplicity and the issues that that raises. But for a co-primary endpoint, where you have to win on both

endpoints, that actually does not present a multiplicity problem. It's quite the opposite. It's more conservative. If you win on multiplicity is when you take alternate analyses for any endpoint or the secondary endpoints. Here, we have four of them. That's a multiplicity problem. The co-primary is actually the opposite. It's more conservative.

DR. FOUNTAIN: All right. So maybe we could take the rest of the questions after lunch, so there is time. It's 12:15 now. We'll now break for lunch. We'll reconvene again in this room in 45 minutes from now at 1:00.

Please take any personal belongings you may want with you at this time. The room will be secured by FDA staff during the lunch break. You will not be allowed back into the room until we reconvene.

Panel members, please remember that there should be no discussion of the meeting during lunch, amongst yourselves, or with any other member of the audience. Thank you.

(Whereupon, a lunch recess was taken.)

DR. FOUNTAIN: Welcome back to the meeting. We'll begin the open public hearing momentarily. I'll read a statement first.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its products, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. But if you choose not to address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully, and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. And thank you for your cooperation in that matter.

Each public speaker will be allowed three minutes. The microphone will turn off after three minutes in the effort of fairness. We really want to hear from everyone.

The open public hearing, where people have important things to say, is valued by the committee, but we have quite a few speakers, so, unfortunately,

we're limited to three minutes. So after three minutes, the microphone will turn off and we'll progress to the next speaker.

Speaker 1, when you approach the microphone, please be sure to tell us your name so we can acknowledge you.

MS. DORMAN: Good afternoon. My name is Diane Dorman. I am vice president for public policy for the National Organization for Rare Disorders. I have no personal financial relationship with Pfizer. However, NORD has received an unrestricted educational grant from the company.

I am here today not on behalf of Pfizer or the product under consideration by this advisory committee. Rather, I am here on behalf of the millions of men, women, and children in the United States affected by one of the 7,000 known rare diseases that, in the aggregate, affect 1 in 10 people in the United States.

Rare disease research in the development of orphan therapies to treat them are unique in many respects. Patient populations are generally very small

and geographically dispersed across the United States, Europe, and Asia. And few researchers and biopharmaceutical companies are willing to take on the financial risk associated with this vital and often life- saving work.

For those reasons and many more, NORD has been dedicated to helping people with rare orphan diseases and assist in the organizations that serve them. We are the primary non-governmental clearinghouse for information on rare disorders, and we are committed to the identification, treatment, and cure of rare disorders through programs of education, efficacy, research, and service.

Today, there are nearly 400 orphan products that treat an estimated 250 rare conditions. Given that there are thousands more rare diseases without any specific treatments, it is easy to understand that there are millions of people who can only hope that, one day, someone somewhere will take on the significant risk to develop a therapy for their condition.

As you deliberate today, I ask only that you keep in mind a few things. Number one, patients

affected by rare diseases are willing to take on a far greater degree of risk than someone affected by a disease that affects very wide populations.

Understanding the pathogenesis of rare disease and the development of orphan biopharmaceuticals to treat them will only increase the medical community's understanding of diseases that affect larger patient populations.

Number three, there are few treatment options available, as I mentioned before, in the rare disease world because orphan products are highly specialized for very small patient populations.

Last, because product development is such a challenge, there is little incentive for companies to develop these products, nor is there much incentive for researchers to conduct basic and translational research.

In closing, I would like to share something a patient advocate wrote to me a few days ago.

"Amyloidosis affects virtually every organ. Any improvement anywhere is a miracle. Our patients are literally dying, waiting for a drug. Perhaps,

please keep in mind that patients affected by TTR are not statistics. A liver transplant should not be a person's only option. And when it comes to risk tolerance in the patient community, the final decision should be made by patients, their families, and their doctors." Thank you.

DR. FOUNTAIN: Thank you. Speaker 2?

MS. GIBSON: My name is Patricia Gibson. I serve as the public policy liaison for the Amyloidosis Support Groups. The Amyloidosis Support Groups have no financial relationship with Pfizer. In the interests of full disclosure, I did attend a patient advocate advisory meeting at Pfizer last year.

In one sense, amyloidosis, being so rare, is an orphan disease, but its full name is familial amyloidosis. It is no orphan when it is carried in the genes of your family, reaching back many unknown generations and is being carried forward into your children and your grandchildren.

Eleven years ago, I watched my husband die of this disease, five years after a liver transplant. Since then, I have been working to find a therapy that

will save my seven children, and my 15 grandchildren, and families everywhere from the ravages of amyloidosis.

Last October, Amyloidosis Support Group gathered over 160 patients with dedicated expert doctors for a two-day emergent session on familial amyloidosis, what it is, what it does, what we can do about it now, and what the future holds. We left with hopeful spirits. A new drug was coming. Maybe there was a chance after all.

We have before us this day the first opportunity ever for a drug therapy to slow or perhaps even stop the progression of this terrible disease. Yes. Liver transplants stop most of the production of the mutant protein. But while you wait for months or years, the amyloid keeps invading your nerves in your GI tract and your kidneys. Soon, you may need a heart transplant. And you know that neither transplant will reverse the ongoing damage that is building as you wait.

Today, we have listened to the analysis of the tafamidis study. There is a question whether the

testing met its mark. In the deep interests of the patients, I ask you to consider that this strategy of the developers of the drug was to stabilize the TTR by preventing the misfolding of the protein.

The test of the efficacy of the drug was to prove improvement in peripheral neuropathy. A number of the subjects achieved a slowing progression in the symptoms of the neuropathy. The efficacy was proved. TTR stabilization was not the endpoint in this study, but is the overriding implicit goal of any drug for amyloidosis.

We have no time. The patients sitting before you have no time to wait. Even now, their amyloid is building. Our children have no time. It makes little sense to deprive them of a safe drug that may slow down the infiltration and allow them to live normally.

I urge you to utilize your flexibility and approve tafamidis.

DR. FOUNTAIN: Thank you. Public speaker number

3?

MR. CLARK: My name is Mike Clark. I live in

Fairfax County in Northern Virginia and have no affiliation with parties involved in this decision.

In February of 2009, my mother passed away from malabsorption, a direct complication of FAP, as amyloid deposits had so invaded her GI tract as to render it inoperative, causing her to literally starve to death.

Her symptoms started some 70 years prior, with alternating constipation and diarrhea, tingling, and numbness that started in her toes, worked up her legs, and carpal-tunnel operations in each hand. After a long story of time wasted with misdiagnosis and incorrect treatments, she was finally diagnosed in September of 2008 with FAP, caused by the T60A mutation of the TTR protein.

She passed away within five months of the diagnosis. Within two months after my mother's demise, I too started having GI symptoms. A DNA screening in July of 2009 showed I had inherited the same mutancy. In fact, three out of four of my siblings have been screened, and all three are positive carriers of the same mutation, meaning there is high probability each

will contract FAP or may have it already. Gratefully, I have not passed this onto my two daughters. However, my oldest sister did indeed pass it onto her oldest child.

This is a disease that wreaks havoc with entire families. Even though I knew the cause of my symptoms, it took until November of 2010 to receive a biopsy that confirmed I was indeed depositing amyloids in my GI tract, but a year had gone by.

The Boston amyloid treatment and research program confirmed the condition, and on April 12th, 2011, I was placed in the Georgetown University Hospital liver transplant waiting list. I have received that surgery as of February 24th of this year. And this is the message I would like the committee to remember from this presentation.

The only tool in the toolbox to fight FAP is the blunt hammer of liver transplant. And it is a mediocre solution at best. Its efficacy is highly dependent on a number of factors, the largest one being how early in the disease progression you can have it done.

It comes with its own significant risks. It does not cure or reverse the disease, as its only positive influence is to possibly stop or slow amyloid deposition. It is life-changing, as you will be on immunosuppressive drugs for the rest of your life, and it is expensive.

We need other options. Tafamidis is the first drug to reach the market specifically aimed at ATTR. And although there is disagreement over the statistical significance of the study's co-primary endpoints, it has been shown to be positive and resulting in stabilizing the TTR protein, as well as other factors.

It needs to be put in the hands of the specialists on the front lines of the disease to treat, study, and find out how best to utilize as a tool to fight this protein-folding disease. I urge the committee to recommend approval of the NDA so that it may be an option when my siblings and niece contract this disease. Thank you for your time and attention.

DR. FOUNTAIN: Thank you. Public speaker number 4?

MS. KLINE: My name is Jorja Kline and I have no affiliation with anyone here or the companies of any kind. I am here as an advocate and a caregiver.

My husband, Gary, was diagnosed with familial amyloid in January of 2007. He participated in clinical trials for Diflunos Boston Medical Center. After six months of being in the trial, he was examined at Lahey Clinical Medical Center in Burlington, Massachusetts, placed on the transplant list for a liver in September of 2007. As he waited for his transplant, his amyloid symptoms continued to worsen. The pain in his hands became so unbearable that he was placed on Cymbalta, Lyrica, and morphine sulfate all at the same time for the intense pain. His ability to walk began to decline. He began to lose feelings in his hands and feet.

Finally, after 20 months from being diagnosed -- actually, 20 months from waiting, and 29 months after being diagnosed, May 22nd, 2009, he finally received a liver transplant. He had to stop all pain medications once he received his liver and had to go on an anti-rejection meds. He went through terrible

withdrawal symptoms, such as inability to sleep for several days, inability to eat, extreme restlessness, continued pain in his hands and feet.

His recovery did go well after that. He was away from work for 13 months. He was cleared to return. However, his position as a mechanic proved to be too much for him and he had to go out on disability. He was unable to stand on his feet for more than 10 minutes at one time. And the neuropathy in his fingers prevented him from doing any of the detailed work he needed to do as a mechanic.

By the end of the day, he was so worn out he could barely even walk to his car. His condition and the quality of his life were fast declining and over such a short period of time since the transplant.

At the end of September, he went out of work on total disability. And by the end of December, he had declined in such a depression that he was sleeping 20 to 21 hours a day. He lost 30 pounds in three short months and had gone down to 130 pounds. He finally started getting some treatment in March of 2011 for both his physical and his mental well-being. However,

during this time, the amyloid did continue to worsen.

Today marks the three-year, two-day anniversary of his transplant. He can no longer stand for any more than three to five minutes. And he can walk no further than perhaps 100 yards. The neuropathy in his hands and feet continues to progress. Some evenings, he has to use Lidoderm pain patches on his hands and his feet to even get sleep. At our house, a good day is when he doesn't fall down more than twice. He has difficulty buttoning his pants and his shirts. His handwriting has become illegible.

A drug as tafamidis shows great promise in improving his neuropathy. And tafamidis can offer relief of pain that comes with this, allow for a more active life, and give the patient the overall hope of a higher quality and longer life. But in the bigger picture, you also have to consider those who may still be coming behind us. Within our family, there are 49 potential people who could develop this disease. A drug that could treat this and keep the terrible effects from developing would be a godsend for everyone.

I ask that you please approve tafamidis. Thank you.

DR. FOUNTAIN: Thank you. Public speaker number 5?

MS. CAMERON: My name is Ellen Cameron, and I have familial amyloidosis, variant ASP18GLU. My familial amyloidosis caused me to have a heart, liver, and kidney transplant back on December 15th, 2005. I have watched my mother, all her brothers and sisters, and my own sister die of this disease. I've seen cousins die while others are waiting for transplant.

I've been one of the lucky ones. Diagnosed, treated, and transplanted by the Mayo Clinic, I was able to move to Rochester, Minnesota with my husband and wait for someone to die to donate their organs.

I would guess many transplant recipients have had their faiths tested. I know mine was. I didn't know whether or not I would see my children marry or have children of their own. I worry about passing this disease onto them.

My variant of amyloid strikes every organ it

can. Since my transplants, I have had five eye operations. I have severe gastric problems. I have tumors in my lungs that makes breathing hard. The neuropathy has caused me piercing pains, any part of my body, without warning. God allowed me to have a new heart, liver, and kidney and they work great. And this is a gift. With this gift, I still have life.

I tell you these things and other things not from ingratitude, not to complain, but to state the facts. On days when the vertigo is bad and getting out of the bed is difficult, my walking is done with the help of a walker or a scooter. I could walk, but I cannot walk straight. And sometimes, people fear that I fall. Sometimes, I do. But I do the best I can, pushing myself so that I do not lose what I already have.

The gastro problems have caused me to wear diapers all the time. It is a very humbling experience, but if you want to get out of the house, I must do what is necessary. This is a disease of coping, cope with fear that this will happen to my children, coping with what I must do to adjust my life.

Another option to organ transplant would help. Not all people are as strong as me or as lucky to have the family support that I have.

I look forward to the development of treating this disease. I look at each of my four children and my five grandchildren and cannot help to wonder whether they will end up with this terrible disease. My prayer focuses on protection for my family and a dream that we will never have the experience similar to mine. Thank you and have a good day.

DR. FOUNTAIN: Thank you. Next is public speaker number 6.

MS. O'BRIEN: Hi. My name is Geri O'Brien, and about a year and a half ago, my family started to be diagnosed with amyloidosis. My husband and two of his siblings have amyloidosis. We have gone from doctor to doctor. We've had great care. And about a year and a half ago, they started telling us that tafamidis would be available to us, and just wait, and hold on. So we were very hopeful.

About three or four months ago, they said to us that that was really all they had to offer us, which

was nothing. And the doctors continued to tell us that the lifespan is 10 years with treatment. Well, we're sitting here with no treatment. We have nothing, but yet we know that it's out there and we know that there's something that can help us.

So I asked one of the senator's offices to help me and he gave me the IND to give to my doctor, which I gave to my doctor. And my doctor said it was too cumbersome to fill out. It needed a review board. It needed to go through the hospital. And it was just too difficult and he couldn't do it. So then I called other people, and they said that the compassionate use was not going to be available to us.

So at this point, I'm asking for compassionate use for my brother-in-law, who is unable to be here, for my sister-in-law, who is unable to be here, and my husband, who is here and will talk.

So thank you very much.

MR. O'BRIEN: Thank you. I just want to add, I'm Bob O'Brien from Long Island, New York. We don't have any affiliation with Pfizer, or any of the committee, or any of that.

I have seven siblings. Three of us have tested positive and have the disease. Two have come up negative, and two have not been tested. My brother, Joe, can't ride a subway or a bus anymore. He's pretty much confined to his apartment, needs help dressing. My sister, Marianne, falls down a lot and is in continual pain.

I'm pretty good. I can still work and was able to get here today. And I was unable to sit here this morning, but if the big objection is the population in the test, I can fill up a study of Irish Catholics from my hometown pretty readily.

I want to thank my Drs. Gorvic, Callman, Mauer, Archer, Papp. They've given us hope. And we see a lot of hope in this drug. If I'm on the committee, as a layperson, I'm asking myself, "What happens if we do approve it? What happens if we don't approve it?"

If we do approve it, a lot of people will be helped and nobody will be hurt. If we don't approve it, nobody will be helped. Research will be stymied and our last weapon of hope really disappears for

another 10 years.

So thanks for the opportunity. Godspeed.

DR. FOUNTAIN: Thank you. Next is Robert O'Brien. I'm sorry, public speaker number 7.

MR. O'BRIEN: Hi, how are you? I'm Bobby O'Brien. Those are my parents. First, I'm going to speak. My aunt from Scranton wrote a little letter and I am going to speak on her behalf. She wrote the following.

"Some of us were cruelly disappointed by the announcement just two days before this hearing, that the FDA's own staff was recommending tafamidis be rejected.

"As laymen and women, we do not know whether such announcements are normally made just prior to public consideration of new medicines, and we sincerely hope politics played no part in upstaging this hearing.

"All we can do is rely on your goodwill and your best judgment, and true interests in what we, not researchers, but the patients and their families have to tell you.

"We understand that tafamidis is not a silver

bullet. We know it will not help all of us or perhaps even most of us. But research on this drug has been one of the very few points of hope for us over the past years.

"It is already being prescribed in Europe, which also has strict standards for this distribution of drugs. When a new cancer drug is developed that can hold off death by even just two to four months, it is approved and heralded as another weapon in medicine's arsenal against that terrible disease.

"Are those few months of a quality of life worth less for the victims of this disease? They do not number in the hundreds of thousands or even tens of thousands, of course. But the suffering of our husbands, and wives, and sisters, and brothers, and parents is just as real. And their disease is also painful, and emotionally crushing.

"And finally, fatal. If this drug helps only the smallest fraction of our loved ones, it will be more than worth it to all of us. It will encourage continued research and keep us hoping for something better, not perfect, not even almost perfect, but

something better the next time around.

"Remember, there are limited effects to this drug, limited side effects to this drug. It won't harm anyone. Please approve tafamidis, even just for the next few years, so we can try it. Please give us this chance.

"Please don't remove one of the first rays of hope we've had in decades. If it doesn't work, God knows we will know that soon enough."

On another note, I spoke with my aunt, Marianne, two nights ago, who is inflicted with amyloidosis. And the two points she conveyed to me was discouragement. She's been battling this disease for years now and she's extremely discouraged and has lost hope. But this drug has reinstated that hope, and her primary worry is her children.

Now, on that note, I love them very much, but I am not here on behalf of my aunts, uncles, and parents. I'm here on behalf of my 19 cousins and we feel that this drug will hopefully increase that research, and increase that push, and hopefully help us as well as our children and our great-grandchildren.

Thank you very much.

DR. FOUNTAIN: Thank you. Next is public speaker number 8.

MR. GOLDSTEIN: My name is Arnold Goldstein. I am 80 years of age, and I have no affiliation or financial interest in Pfizer.

In 1994, I was diagnosed with atrial fibrillation. And then in 2000, I had a congestive heart failure. And between 2000 and 2003, I had stents and a Pacemaker.

In 2007, I was biopsied and diagnosed with wild- type transthyretin amyloid cardiomyopathy, the familial type, senile type. In 2008, I was fortunate enough to enter the New York Presbyterian FoldRX test program for tafamidis meglumine, FX1006A, overseen by Dr. Matt Maurer. Between 1994 and 2007, I had two carpal tunnels, several trigger fingers, which I'm told is not unusual with people who have amyloidosis.

However, since taking tafamidis, I've had no further trigger finger symptoms, nor atrial fibrillation, or heart failure. In addition to tafamidis, I'm taking a number of other drugs, the

usual roster, eplerenone, amiodarone, aspirin, simvastatin, ramipril.

For the past four years, I've been experiencing significant sensations of pins and needles in both feet. I have been informed that this is not unusual for people with amyloidosis. It is my understanding that the disease gets progressively worse as time goes on and, if left untreated, could prove to be fatal. I am not aware of the statistics, but I'm told that without tafamidis, I probably would not have survived the last five years.

While it is stressful climbing stairs or hills or sleeping with only one pillow, I'm able to live a normal life. I go to work four days a week, do mild exercise. I'm able to socialize with friends and family. I therefore believe that tafamidis, while not curing the disease, has most probably restricted the disease's progress.

In closing, I would like to thank Dr. Kelly for the work he has done in developing tafamidis and its continuing work in combating this terrible disease. Thank you.

DR. FOUNTAIN: Thank you. Next is public speaker number 9.

MR. MUI: Hi. My name is Kevin Mui. I'd like to thank the committee for the opportunity today to share my family's history and my experience with familial amyloidosis.

It began with my mom, Sue Mui, when she was 40 years old. At that time, we didn't know much about amyloidosis and there were no treatments available for her. She suffered for six years and we lost her at the age of 47.

Later, her brother, Ed Young, was diagnosed. It was then we learned that liver transplant could be a cure. He underwent the liver transplant, but the disease progressed. He survived 10 years and we lost him at age 45.

Then again, my brother, John, was diagnosed at age 35. We thought, if we were proactive in getting him a liver transplant earlier, while he was younger and stronger and before the symptoms really set in, that would stop the disease. But again, although the

transplant was a success, unfortunately, his symptoms overall did not improve. Neurosymptoms developed and continue to challenge him today.

I was diagnosed at the age of 31 three years ago with ALA 71. Knowing my family's history, I did everything I could do to build up my body stronger to help defend myself against this disease, but I was surprised how quickly symptoms develop and how debilitating it can be.

The first year after diagnosis, I lost 80 pounds due to severe diarrhea and loss of appetite. I suffer from bouts of dizziness, numbness in my feet, legs, and hands. With my energy zapped and severe muscle loss, I can no longer perform the physical activities I once loved and eventually had to leave my job, as I could no longer manage the demands of my career and be a full-time patient juggling these symptoms.

Today, I am 34 years old. Performing daily activities and simple tasks like climbing stairs, getting showered, or even dressed is becoming a challenge. I am getting weaker and more limited,

despite my ongoing efforts with physical therapy and even seeking alternative medicine like acupuncture.

This disease doesn't just cause physical pain. It also destroys many of my hopes and dreams. I am losing control over the basic things in life. How can I plan for any future? I wonder if I can still pursue my dreams, return to work, or maybe have a family of my own one day.

I am here today to ask you to support the approval of tafamidis. Time is not on my side, but I am hopeful that this new drug, even if it's not perfect today, can help keep me and many others coping with familial amyloidosis alive while scientists, doctors, and patients work together to gain a better understanding of this drug's effectiveness, not only through treating peripheral neuropathy, but also understand its effects on other crippling symptoms that affect our heart, our eyes, the autonomic nervous system, and more.

Again, please approve tafamidis today. We are in desperate need of a miracle. Thank you.

DR. FOUNTAIN: Thank you. Public speaker

number 10?

MR. SUHR: Good afternoon. My name is Dean Suhr. I am humbled by all of the prior speakers who are directly affected by this disease. I have no financial interests to disclose. However, I am a rare disease dad. I have metachromatic leukodystrophy in my family, not even related to this, a much more rare disease. I'm president and co-founder of the MLD Foundation and I'm chairman of the patient advocacy advisory board for the Rare Project, representing the 1 in 10 Americans with rare diseases.

We've heard about this disease today, and we know that it's devastating. It affects about 2500 people in the United States. Only 350 of those people apparently had been identified. There are a lot of patients in this country that need the services here.

But there seem to be two criterion in play. One is primum non nocere, do no harm. That's the foundation of the work that the FDA does. That's the reason that you all sit, and deliberate, and work through all of this. And the second is the facts.

The facts that we do know in this disease is that death, which is 100 percent mortality, is 10 to 15 years without therapy. And we have heard about the liver transplants. The mortality on that is 10 percent right out the gate for a liver transplant, and goes up to 30 percent for a 10-year lifespan, and even higher when you have the cardiac involvement. Of course, there are inconveniences with immunosuppressants and those sorts of things.

So the alternative with this disease is devastating. Today, we're using statistics to decide the safety and efficacy of this drug, and that's how all of your regulations and all of your rules are put together. But that's interesting is what's driving the statistics. As we've heard in the conversations, and the questions this morning, and I imagine we'll hear this afternoon, it's not the statistics that are the issue. It's the assumptions on the facts. Did those people leave the program because of something unusual related to liver transplants? It's group A, group B, what country, and so on, and so forth.

So the facts themselves -- as Mark Twain

says, "The facts are stubborn, but the statistics are much more pliable." We can work these statistics to be within the regulations by not adjusting the facts, but by how we choose to interpret the facts.

We've heard a lot about the studies here. The real question is, is the 005 study indicative and does the 006 study add onto it or not? And you all need to work through that. You're much more intimate with that.

But what the sponsor has asked for today is to be able to participate in the accelerated approval of subpart H, which does require your ongoing supervision. So while families could get therapies and treatments, you would be able to supervise that through ongoing trials, which the sponsor has acknowledged that they would certainly accommodate.

Rare diseases do not ask for nor do we deserve a pass on all the rules and regulations. But the reality is that the risk-benefit tolerance for the families with these diseases, kids, relatives, spouses all dying, our risk tolerance is much higher.

There was a full-day session on this at the

FDA last Friday, talking about this particular issue. The diversity in those studies is very difficult to do as rare diseases because the patient populations are small and you need to take that into consideration.

So I ask that you do no harm and that you consider approval of this and the ongoing monitoring with subpart H. Thank you.

DR. FOUNTAIN: Thank you. Next is public speaker number 11.

MR. MCGARRY: Good afternoon. My name is Martin McGarry. I stand here before you, representing five siblings, four children, five grandchildren, 26 nieces and nephews, 42 nieces and nephews, grandnieces and nephews, many cousins in the United States, Ireland, England, and the memory of my mother, two brothers, an uncle, and a cousin who have passed away from amyloidosis as a result, as all of those who are or who have been affected by this disease as well.

I was born in County Mayo, Ireland, the youngest of eight children. I came to Chicago in September of 1969, when I was 18 years old. I worked in the construction field. I am a former professional

amateur boxer, boxing in England, Ireland, and the United States.

In 1976, I married my wife, Kathleen. We had four children within the next 10 years. I was a very active parent, helping coach my kids in various sports. My two oldest brothers, John in Chicago and Pat in England, and my mother in Ireland all became ill at about the same time, the early 1990s. They had chronic diarrhea, were losing weight, and had neuropathy in their legs, affecting their mobility.

After a few years of surfing, John was diagnosed with amyloidosis in 1998. He had a heart and liver transplant at Mayo Clinic in 1999, but the disease had done a great deal of damage to his body, and he died after three years, in 2002.

My brother, Pat, was diagnosed at about the same time and had a liver transplant in London. He also lived for three more years and died in 2003.

My mother died in 2002 of the suffering with neuropathy and for many years as a result of amyloidosis. Her older brother died of the disease about 10 years before her.

I have first cousins with amyloidosis in County Mayo, Ireland. One died a year ago. His two brothers have been diagnosed recently. This past summer, I started to lose weight. My legs started to get tired after jogging a short distance. I have always been physically active. I work out regularly. I'm a certified amateur boxing coach and trainer. I coach boxers. I spend a great deal of time working with young men and women, helping to develop their boxing skills.

Knowing the health history of my family, I suspected that this might be the beginning of this terrible disease in my body. I found out about an amyloidosis conference last October. We went to find out more about the disease. We learned a lot about amyloidosis and the latest research for a cure. My blood was tested and I found I was positive for ALA 60. I also had a fat tissue biopsy that tested positive for amyloidosis.

I went to Mayo Clinic for more extensive tests. I was given three options, do nothing and hope for the best, have a liver transplant, or wait for a

medication that may come on the market.

My first option would be for the medication. None of my brothers had good luck with their transplants and I can't sit around without doing anything, knowing that there is research being done now, working to find a cure.

As of now, I have neuropathy in my legs. My energy level is diminished. I feel that, if there is a drug to control amyloidosis, I will travel anywhere to obtain it.

Time is of the essence for me, my family, and everyone who is affected by this disease. Thank you.

DR. FOUNTAIN: Thank you. Public speaker number 12? Public speaker number 12?

(No response.)

DR. FOUNTAIN: How about public speaker number 13?

(No response.)

DR. FOUNTAIN: Public speaker number 14?

MS. PIRES: Good afternoon. I am Natacha Pires with the Neuropathy Association. I have no

financial relationship with Pfizer. Pfizer has and does provide grant support for the association's programs.

I want to thank everyone here for recognizing the challenges of the 20 million Americans whose lives have been devastated by a neuropathy diagnosis and particularly by transthyretin familial amyloid polyneuropathy, or FAP. FAP is a progressive and fatal form of neuropathy, affecting approximately 2500 patients in the U.S. For them, no pharmacological therapies exist. FAP is caused by mutations of the TTR gene, causing buildup of abnormal protein in the peripheral nerves, as well as other organs.

For most patients, the first symptoms occur during the third or fourth decade. Typically, patients present with sensory motor neuropathy. They also develop autonomic neuropathy, impacting vital body functions, including blood pressure, heart rate, bowel and bladder emptying. Over time, the gastrointestinal involvement results in weight loss, loss of muscle mass, physical wasting, and ultimately leading to death.

Currently, FAP patients in the U.S. have only one interventional therapy, liver transplant. A liver transplant removes the abnormal protein from the circulation and stops amyloid deposition.

Patients who are fortunate enough to receive a transplant also face significant transplant-related morbidity and mortality. Without a transplant, FAP is fatal. It's a death sentence, usually within a decade, unless these patients move to Europe where tafamidis is an approved therapy.

All the more reason to consider the potential benefits of indicating tafamidis for FAP, this gives physicians one more tool to help patients, and it gives patients access to a life-saving therapy that addresses the underlying neuropathy.

With 20 million Americans living with over 100 types of neuropathy, 6 million with chronic neuropathic pain, our community is underserved. We have only seven FDA-indicated therapies, one for CIDP, and the remainder for diabetic neuropathy, and post-herpetic neuralgia. This helps about a third of our patients, which begs the question, what are the other

two-thirds supposed to do? What are the 25 patients with FAP supposed to do?

Thanks to the tireless efforts of researchers and advocates alike, we continue to discover new therapies with potential to give our patients a fighting chance. This meeting recognizes the significant unmet needs of people with FAP and our broader neuropathy community. Please consider the possibilities as you review the data presented today. Thank you.

DR. FOUNTAIN: Thank you. Next is public speaker number 15.

MR. [redacted]: Thank you, Mr. Chairman and members of the committee. I appreciate very much your willingness to listen to me and the other sufferers from this disease.

DR. FOUNTAIN: Excuse me. Can I ask you to state your name? I'm sorry to interrupt you, but if you could, state your name before you begin.

MR. [redacted] I'm so sorry. I'm [redacted]. I'm number 15. I appreciate very much your willingness to listen to the patients in addition to the medical

and pharmaceutical experts. And thank you for that.

I did figure out this morning that QOL must mean quality of life, and mine is going downhill. I used to be a runner and now just walking is sometimes difficult. But when I really jumped was when Dr. Coelho this morning referred to this problem as calling "severe progression invariably leading to fatal outcomes." And that's not statistics. That's me dying. I just can't stress enough how I know you all know it, but how important this is to those of us who have this problem.

Without a pharmaceutical solution, I have either a transplant or I have death. And I'm being treated at two of the top amyloid centers in America, and they both agree on that.

We have a drug here that's been extensively tested in Europe and it's been approved by presumably knowledgeable people in Europe. And my hope is that, that accounts for a lot. I'm sure Dr. Farkas is right, that there are statistical issues that ought to be sorted out, but my hope is that we can begin to use the solution that the Europeans have identified, including

the last six months apparently of very small side effects in Europe.

If this drug had just popped out of Pfizer's lab, I wouldn't be here today. It would be a waste of time. But here, the testing and the background, it seems to me, puts it in quite a different perspective from the point of view of approval or at least some kind of a partial approval.

So my purpose in being here today is to ask you to help the thousands of people who suffer from this and related amyloid problems by some kind of an approval so that we can begin to move ahead on some sort of a high- speed track.

I don't know all the rules of section H and this sort of thing, but to begin using it in America, and then benefitting from the testing that's already been done, and benefitting from the testing that would be done as we move ahead.

A liver transplant or dying is a terrible option for me. I was very impressed as I came in to see the poster that you have up of the FDA's efforts on orphan diseases. And I just think it's wonderful that

you're focusing on that. And I commend you and I hope that you will help with this one, too.

Thank you very much for your consideration of all of us and I appreciate it.

DR. FOUNTAIN: Thank you. Next is public speaker number 16.

MS. PRETE: My name is Kristin Prete. I have no affiliation with Pfizer. I am here today in honor of my father, Anthony, whose life was claimed by FAP exactly one year ago tomorrow after enduring a decade of anguish and agony.

After years of misdiagnoses, unnecessary surgeries, and treatments, he was finally diagnosed in 2006. Dr. Skinner at Boston claimed he was one of the most severe cases she had seen. Despite already six to eight years into the disease, a liver transplant in 2007 was his only option. He only waited five days on the transplant list, luckily, but he sustained significant complications and the disease continued to progress.

My dad suffered almost all of the known symptoms of Met 30 FAP before dying, many of which have

been mentioned today. Paralyzed and bed-bound, he suffered syncope episodes, required a Pacemaker, a fully catheter, a feeding tube. He had vitreous opacities and double vision. He lost well over 100 pounds in just a few years, and had multiple hospitalizations, and unbearable pain.

He mourned at the loss of his hands the most. He often quipped that he would cut off his legs if it meant getting his hands back. He was a writer, a Biblical scholar, and a teacher, and spent most of his days at the computer. His voice-activated speech recognition program rarely worked well and as his voice began to weaken, it caused frustrating problems.

He was locked out of the outside world, unable to e-mail or read the news. He was unable to hold a book, or a newspaper, or a magazine. He was unable to operate a remote control. He needed someone with him all the time.

The most unbearable part of this was the emotional pain. Psychologically, he was just as broken as his body. He had lost everything, his body, mind, spirit, independence, all he enjoyed, and even his

faith in God after dedicating a lifetime to God. It had also exhausted my mother and all of our family's finances.

Make no mistake, this disease is wretched and far-reaching. Exacerbating his mental anguish was finding out that his brother and sister, his only siblings, were also diagnosed, his brother already developing symptoms. His cousin was diagnosed. And then finally his only biological child, me, was also diagnosed.

This is a disease that wipes out families, as you have heard from many who have testified today. I am a grieving daughter and a fearful victim. I am a mutant, but I have no special powers like in the movies. My only power being exerted here today is my attempt to persuade you to pave the way to save my life, to save my family, and to fight for all who suffer, who have few or no options to avoid the horrific fate my father faced, so that his death not be in vain.

Any treatment is better than a transplant in my opinion. I know this is not a panacea, but it is

safe, and it brings hope and help to those who cannot wait, and will pave the way for future therapeutics and hopefully a cure.

We are on the precipice of minimizing, if not ending, intolerable suffering for thousands. While you all are not mutants, you too have special powers and can be heroes. All you have to do is open the door. Thank you.

DR. FOUNTAIN: Thank you. Next is public speaker number 17.

MR. ROBINSON: Hi. My name is Darren Robinson. I am not affiliated with Pfizer or anything. I am here on behalf of my uncle. He's just recently been diagnosed with amyloid TTR, and he's suffering at this moment. He's not a candidate for a transplant, but I only recently found out about this a few days ago and he's only been diagnosed a month ago.

So I'm here on behalf of my uncle to state to everyone here that the opportunity that you have in front of you, as we've heard and I've sat here and heard, I know there's thousands of people out here that need this. And I'm asking the panel to please consider,

because there are people that are suffering right now in the hospital, as well as my uncle. And it's overwhelming. And my family doesn't know. It's new to us, so we don't know what stages, and all the things, and tests that we have to go through.

I have a five-year-old grandson. I have my mother, my uncle. My uncle is here, my brothers. I have family members, so I'm here on how it affects the family.

So I'm here on behalf of him to just ask you to, please, if there's any other way -- excuse me. It's out here. It's helping people. There are people dying today right as we speak. And my uncle has no chance with a transplant, but if this medication can sustain him a few more years to be with us, then I'm asking you people to please do what's necessary, pass this drug, so that it can help thousands, millions of people in the future. Thank you very much.

DR. FOUNTAIN: Thank you. And thank you to everyone who made public comments. I know it can be difficult to speak in public about such personal issues and the committee appreciates it.

The open public hearing of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We'll now proceed to the questions to the committee and panel discussions. I'd like to remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be

displayed on the screen. And the DFO will read the vote from the screen into the record. Next, we'll go around the room. And each individual who voted will state their name and their vote into the record.

You can also state the reason why you voted if you want to. We will continue in the same manner until all questions have been answered or discussed.

So we'll turn our attention to the questions.

Does anyone need to follow up on any of the questions to Dr. Farkas before we begin the discussion, since we cut off that early? Dr. Gooch?

DR. GOOCH: This is a clarification, which will relate to part 1A. This has to do with the FDA rules regarding subpart H, and perhaps Dr. Katz or one of the other FDA staffers could help to clarify this for me and perhaps for some others.

How much flexibility is there in terms of a situation in which the primary endpoints of a study are not met under subpart H? And then that's my first question.

Then the second is if we could just have a brief review of the regulations regarding the

consideration of surrogate endpoints. It was gone over this morning, but just a capsule summary before we begin the deliberations.

DR. KATZ: I'll take a stab at part of that. As far as the flexibility, I think the first part of your question was the flexibility in p values with regard to subpart H.

DR. GOOCH: Yes.

DR. KATZ: As we were talking about this morning, the rules -- or the standards for approving a drug for subpart H are the same for any other type of approval with regard to the effect on the surrogate that you're talking about. So subpart H means, in effect, on a surrogate that is reasonably likely. We don't know it's going to predict, but we think it's reasonably likely.

There has to be substantial evidence of effectiveness for the effect on the surrogate, whatever the surrogate is, whether it's a lab test, whether it's a clinical outcome.

So the same standard for substantial evidence of effectiveness for any other type of approval, just a

regular approval based on a clinical outcome, no surrogate involved, the same degree of substantial evidence of effectiveness has to be found for the surrogate under the subpart H rules.

So as we discussed, there are really two ways to get to substantial evidence of effectiveness. One is at least two adequate and well-controlled trials where a statistical significance is achieved on the primary outcomes. Statistical significance is usually, almost always, considered to be a p of less than .05, two-sided p. We can talk about that, but the traditional standard for two studies is the p less than .05 on the outcomes for both studies.

The other way to get to substantial evidence of effectiveness is one adequate and well-controlled study plus something called confirmatory evidence. In that case, when there's only one study, you really want the results of that single study to be very robust. And you saw, I think, Dr. Farkas showed a slide and I talked about some of the elements of a single study that would make it very robust, like a very low p value, so maybe a p of .01, or .001, or something along

those lines, multiple subsets going in the same direction at multiple centers, multiple study sites going, all being positive.

Confirmatory evidence could come from that study itself if it's extremely robust, everything moving in the right direction, including low p values, or confirmatory evidence could come from some other outside source. But you have to have substantial evidence of effectiveness for the surrogate. And that substantial evidence standard is the same as it is for any other kind of approval.

So then you have to take the extra step from the point of view, if we're talking about subpart H, that you have to conclude that the effect on the surrogate for which you have to have substantial evidence is reasonably likely to predict the outcome of interest.

We can talk about what reasonably likely means in any given case, but it often involves a detailed understanding of all the effects of the drug and a detailed understanding of all the events and the disease that produce symptoms, so you can be reasonably

likely that the effect you see on the surrogate will have the clinical effect that you care about down the road.

So that I hope answers your question with regard to the first part. I no longer remember the second part.

DR. GOOCH: So thank you. That does clarify the rules regarding the surrogate evidence in the case of a single study approval. In any case, though, the primary endpoint measures must be met. Is that correct?

DR. KATZ: We're talking about subpart H? It doesn't really matter. Again, in subpart H, the primary outcome could be a lab test or something. But yes. We would routinely expect that to be the case unless there is some compelling reason to look at another analysis, in other words, with a primary analysis, which in this scenario fails to meet the usual rules of statistical significance, where we find that that analysis was wrong, it was chosen poorly, the data don't allow that analysis to be done, some compelling reason to move to a different analysis than

the one that was prospectively designated. And there can be circumstances in which that is the case.

DR. FOUNTAIN: Dr. Mielke? I'm sorry. Yes.

DR. MIELKE: I have a question following up with that. Again, kind of regarding the flexibility, there was a mention in terms of orphan drug status, that there is a little bit more flexibility with a .05 p value.

So how much flexibility is there? What would be the confidence interval, I guess, around that? That's one of my questions.

Then the second question is, getting back to the analysis of secondary endpoints and multiple testing, there are a couple ways to look at it. If the directions are all very similar for the secondary analyses, even if they're not all significant, is that still sufficient evidence, I guess? Would that be considered?

DR. UNGER: In terms of orphan diseases, we do have a license to be more flexible and we certainly try to be more flexible. But in terms of how the flexibility is spelled out in the regulations, it's

really not.

So we still need substantial evidence of efficacy, as Dr. Katz told you first thing this morning. So it's not clear exactly how we carry out this increased flexibility, but whatever it is, we try to do it.

In terms of the secondary endpoints, I mean, at the end of the day, when one integrates all the evidence of effectiveness and all the safety data, it's a judgment call for us. And I guess that's where the extra flexibility comes in. And that's why it's not written down anywhere what that actually means.

So when we gauge all the data, the fact that it's a co-primary endpoint, it didn't win on either component, but if you do alternative analyses, they can win the multiplicity in the secondary endpoints. We have to put all that together, hopefully with the help of your discussion here in the next couple hours and try to figure out what it all means.

I don't know if that answers your question and Dr. Katz might want to add something.

DR. KATZ: Yes. It's sort of impossible in a

vacuum to answer the question as to what the required p value is for an orphan. As we've said, for an orphan disease, there needs to be substantial evidence of effectiveness. And that's usually defined in the ways that we've defined them already a number of times. We have to convince ourselves -- the point here, I think, is that, again, there's a traditional standard we all know at .05, in two studies something less than that, in one study with everything else, if it's one study, going in the same direction, hopefully some nominal significance in some of those outcomes.

That's sort of what we take. Let's take the traditional non-orphan, non-surrogate, just regular approval, two studies, .05. That provides us with a certain amount of confidence that the effect is real. That's the goal, whether it's a subpart H approval, whether it's one study plus confirmatory evidence approval, whether it's an orphan product. We need to be able to conclude that the effect that we saw was caused by the drug, and not chance, and not biased, and not fraud, of course.

So we have to convince ourselves that the drug has produced the effect that we have seen. The usual standard that we apply is the one we've talked about. Anything less than that, we're less confident about.

As Dr. Unger says, if it's not exactly according to the usual rules, we look at everything else and we just try to convince ourselves that the effect that we're seeing is not due to bias or chance, that it's related to the drug. And it's hard to give you a number.

DR. FOUNTAIN: Thank you. Dr. Clancy?

DR. CLANCY: This is also a question for Dr. Katz regarding flexibility. So the .05 number is sort of a standard number for any kind of a statistical analysis, and you want to be sure that differences between the two groups aren't just statistically fluked. There's less than 5 chances in 100 that it's just a fluky thing.

I wonder if the FDA would be flexible enough to consider a real focus of treatment effect, though,

on the efficacy evaluable patients. We started off with a lot of patients. Very few dropped out for small reasons, a couple pregnancies, having adverse effects. Almost all of the dropouts were for the liver transplant. And there's an old Quaker -- you take the cookies while they're passed. If someone offers you a liver, you take a liver right now. You don't wait around for the end of a drug.

If you want to know it's real, those patients, though, treated in the intention to treat are treated as failures, and yet we don't really know they're failures. We're assigning them that value, but some may have improved and some may not have.

So the question I want to know is, if a patient has the disease, and takes the drug, and stays on the drug, are they or are they not better at the end of that time? And to me, the answer is yes. It looks like it is.

So would there be flexibility enough to weigh the intention to treat classic population analysis for, in this specific scenario, efficacy evaluable patients?

DR. KATZ: Yes. All this can weigh in, but I

think that the short answer is, is there flexibility to rely on an analysis that wasn't a prospectively designated analysis -- the prospectively designated study population in the protocol? Yes. There is flexibility to do that. The question is, is it appropriate to do so? And that's one of the questions we have for the committee.

By the way, I have a question for the company specifically about this point, which I think is very important. I can ask it now.

DR. FOUNTAIN: Why don't you ask it?

DR. KATZ: The analysis that we have seen, that presumably -- it might have been slide 80; there might have been other slides as well -- that presumably takes into account the fact that a lot of the dropouts were due to a liver transplant, was presented as the efficacy evaluable analysis. It was a nominal p value of .041 or something.

The term "efficacy evaluable" or "evaluable patients" usually includes -- and I think it did here, too, and if I'm wrong, tell me. But it usually includes a whole bunch of folks who left the study

early. They didn't complete, they only took 80 percent of the prescribed drug. There's a whole series of things. So we don't, as a general matter, like those sorts of analyses because those folks could have left related to the treatment somehow.

So I'd like to know if that analysis was that type of an evaluable patient analysis or was it an analysis just with the transplant patients excluded. If it's not that analysis, do you have an analysis where you just excluded the transplant patients and included everybody else? Let's call it a modified intent-to-treat in that sense, because I think slide 80 is the more traditional evaluable patients, where a bunch of people are not included.

I could be wrong, but I think it'd be a very important point because everybody is saying the evaluable patients analysis is the real analysis, but I'm just not sure who was included in that analysis. Maybe we can get that clarified.

DR. GROGAN: Sure. We specified the efficacy evaluable population as those patients who completed the full 18 months' treatment per protocol. So the

majority of patients who dropped out of the study were due to liver transplant.

But however, we looked at all the patients who completed the full 18 months of treatment. 91 patients completed the full 18 months' treatment and two additional patients from each treatment group, who we believed and were assessed prior to unblinding, had important protocol deviations. They were dropped from the efficacy evaluable. So almost all the completers were included in the efficacy evaluable.

The rationale for that in this pre-specification is, for disease-modifying therapy like tafamidis, you really want to follow patients across the full 18 months of treatment. If there is a true treatment effect, the placebo patients would worsen over that 18 months' period of time and the tafamidis patients would worsen less or not worsen at all.

So the reason why we pre-specified this analysis is we wanted those patients who were able to complete the full 18 months on therapy. So again, we do believe that this does represent the treatment effect of tafamidis as we've presented in the totality

of the data.

DR. KATZ: But it's not -- again, what I'm calling, defining here, the modified intent-to-treat now, it's not everybody except the transplant patients. Correct?

DR. GROGAN: That's correct.

DR. KATZ: Do you have that analysis?

DR. GROGAN: Not in that way. What we had and what's included in our file is the sensitivity analysis that, instead of calling the liver transplant patients non-responders, we imputed their response, should they have stayed into the trial for the full 18 months. That's the sensitivity analysis of the NIS-LL responder analysis.

Perhaps I could ask Dr. Schwartz to come up and give you just perhaps a little bit more detail on that.

DR. FOUNTAIN: Can I clarify something, though, as part of that? So that means there were 125 people. 91 of them were in the efficacy evaluable group. And 26 had liver transplant. So that leaves six that were included that didn't have liver

transplant.

Does that sound numerically accurate?

DR. GROGAN: There were 87 patients in the efficacy evaluable population.

DR. COHEN: Eighty-seven.

DR. SCHWARTZ: Maybe I could provide an alternative analysis that gets at what you're asking for. The NIS-LL change from baseline to month 18, a key secondary analysis, on the intent-to-treat group, uses all the patients, including the liver transplant patients up to the time at which they dropped out for liver transplant.

So there were no exclusions for the other criteria that are usually the case in efficacy evaluable. So we have those analysis results as well and those are significant.

DR. KATZ: We can talk about whether that's the perfect substitute, but again, just to get back to your question so it doesn't get lost, is there flexibility? Sure. But the question is -- and this is the case -- is it appropriate to focus more on the efficacy evaluable population than it is to focus on

the protocol-specified analysis? And we'd like to hear your views on that.

DR. FOUNTAIN: I have a question for Dr. Farkas. I was a little confused by the presentation of some of the analysis which you suggest maybe the differences were due to chance rather than actually statistical differences.

But did your overall analysis identify any things that didn't change in the right direction? It looks like, from the data that I've seen, things all seemed to change in the right direction or be neutral, rather than changing in the wrong direction, even though it wasn't statistically significant.

DR. FARKAS: Yes. I think that's a fair statement. I mean, I guess that -- if there weren't small changes -- this is going to sound a little bit negative, a negative world view. But if there weren't small changes in a positive direction -- sometimes it doesn't help to know if it -- we wouldn't be here today, even if by chance there were changes in the wrong direction.

So I guess that I'm not quite sure personally

how reassured I am by that, because there's other studies that fail. Studies sometimes show, again by chance, that the drug is inferior to placebo. I think in our guidance about efficacy, it explains that, that if we just went by the .05 p value standard and none of the drugs that were tested had any efficacy, then we would approve 5 percent of them. So I think that's just, again, a consideration.

DR. FOUNTAIN: Yes. So my question wasn't about the statistical significance, just about the trends, the numerical differences between groups.

DR. FARKAS: Right. Anyway, I think that pretty much things were numerically in the right direction.

DR. FOUNTAIN: Next, Dr. Shefner?

DR. SHEFNER: I'll just respond to this point before I raise my point, which is that on slide 84 from the sponsor, where responders are broken apart by initial baseline level, those subjects that were least affected at baseline, actually had changes in the opposite direction, at least as I read that study, that the responder rate was higher in the placebo groups for

those patients than it was in the treated patients. So there is that, anyway.

What I wanted to just discuss a little bit more is this idea of flexibility in orphan diseases. I've spent my career looking at and trying to treat patients with an orphan disease that is fatal in about half the time that this disease is. And I have come to the view that, that doesn't change your need for certainty or at least confidence that what you're observing actually is real. But I have looked at study, after study, after study with near statistically significant p values in phase 2 and been very excited by them. I've also seen many studies where virtually all of the outcomes were near significant in that direction, only to be disappointed by the phase 3 studies.

As a sideline, this in terms of absolute numbers is a very small study that would qualify as a phase 2 study in most more common diseases. And so I just think that we have to be focused on the confidence level that we have.

I personally feel that there's a big question

in that regard. And so the flexibility that we're talking about, I think also reduces our ability to be confident.

There was a question buried in there somewhere. And the question was that, in addition to this flexibility, the lack of hitting the primary endpoint, one other big potential problem is that more than half of the patients were enrolled at one site. And we've been told that if you take those patients away, there's no signal. But I haven't seen any data, so it would be very useful to me to actually see the numbers of this analysis on the patients that were not from that site. I don't think we saw that.

DR. FOUNTAIN: Could I ask the sponsor to pull up those numbers while we're answering the other questions? I'll give you an opportunity to do that.

So to rephrase your question, you want to know the primary endpoint efficacy analysis, separated out by this single site that's high-enrolling compared to all the others.

DR. SHEFNER: Right. I mean, the side that was presented was efficacy by site, but I didn't see a

combined analysis of all other sites besides the single one.

DR. GROGAN: Yes. To do this analysis, we looked at the continuous change from baseline across all of the endpoints. And we grouped Porto, the highest- enrolling site, and all other sites together. We showed you the analysis that we had, the by-site analysis, and we have all those for all the endpoints.

But if I could see slide AH1, please? So I showed you the point estimates slide, which had the full population. This is a very similar slide that I showed in our main presentation, for which we conclude that the results across all these various endpoints, all numerically, and many statistically, support the effect of tafamidis across these various measures.

So the top panel is the point estimates and the 95 confidence intervals for Porto. And the bottom is the same assessments for the other sites. And you can see, except for sensation and reflexes on the line, we have similar directionality, obviously very wide error bars. These are small populations.

As you mentioned, this is a small study,

although it's a large study for this very rare disease. And then when you start dicing this population into even smaller and smaller groups, obviously, you're going to lose significance, but at least the directionality is the same.

DR. SHEFNER: Thank you.

DR. FOUNTAIN: Is there a response to that relative to this slide and this question? Dr. Cohen?

DR. COHEN: I deal with ALS, too, and we really do want to have therapies, but like Jeremy, I'm slightly hesitant. Looking at this -- and probably I didn't ask this question correctly. But just clinically taking care of patients with FAP, on the NIS-LL, the major component that's causing that to go in the best direction is probably the muscle weakness? That's improving?

DR. GROGAN: Correct.

DR. COHEN: So medication has most profound effect on weight or BMI measure, as well as quality of life, as well as muscle weakness?

DR. GROGAN: Yes. And I would say, actually, from a point estimate, similarly for summated seven

score, I think the point estimate is very similar to the NIS-LL.

DR. COHEN: So things that are very troublesome to the patients and limit activities of daily living like sensory deficits, autonomic syncope, that really is not coming out in this analysis?

DR. GROGAN: Well, again, when you dice this population into a smaller population, you do see, at least at the Porto site, that you have significant difference between the treatment groups in sensory and also very close to reflexes.

DR. COHEN: Just, I'm not saying you should, but if one takes Porto out, then it's not. Okay.

DR. GROGAN: Yes.

DR. FOUNTAIN: Yes, Rusty?

DR. KATZ: Yes. Just, if I heard you correctly, at least for the NIS-LL, I don't think that was the primary outcome. If you look at the primary outcome, the responder rate, I have it on page 12 of my memo -- I assume I got the numbers right. You tell me if I didn't. But if you look at the non-Portugal sites

in responder rate, the responder rate on placebo is 32 percent and on tafamidis is 25 percent. So it's in the wrong direction, not whoppingly in the wrong direction, but it doesn't seem to have --

DR. GROGAN: Right. I would like to sort of address that and have Dr. Schwartz come up as well, but one of the things we've learned from this program -- and I think this is often the case in rare diseases -- is, you start the trials and you're dealing in programs with the best information that you have.

Sometimes, that's flawed. And I think it is clear now that the dichotomous reduction of this NIS-LL continuous variable is probably not the best method of analyzing this endpoint. And I think the continuous change variable that we analyzed is probably a better reflection of a true treatment effect.

But I'd like to have Dr. Schwartz just talk about the responder, non-responder analysis.

DR. SCHWARTZ: So one of the issues that we wrestled with, with the responder analysis, is how it behaves at the different sites. There is a significant site-by-treatment interaction when we look at the

responder analysis and we put a site-by-treatment interaction in the model. But if we look at the change from baseline analysis, the site-by-treatment interaction is not significant. The p value for that test is .2406.

So this is the analysis of the change from baseline, looking at the site-by-treatment interaction. The site-by-treatment interaction term is not significant, although the pattern appears what we would call a quantitative interaction had it been significant, meaning that the directionality of the differences are still preserved. The tafamidis group is still showing a better response than the placebo group at the Porto site, as well as at the other sites, although the differences are much narrower at the other sites.

DR. FOUNTAIN: Anymore discussion of this question and this specific topic?

DR. FARKAS: So we actually had p values for the site 1 versus other sites. And the actual p values -- or the analysis that we saw -- I don't know if that gave the committee all the information that they needed

because it was in kind of a different format, I think, than some people are accustomed to looking at.

So I guess the question would be if any committee members thought that they wanted the p values from site 1 versus the other sites.

(No response.)

DR. FOUNTAIN: I take that to be a no, unless that's a comment.

DR. PRESTON: Yes. Just a comment about the p value and the latitude in the p value -- everyone knows this. But a p value of .05 is an arbitrary set value. I understand this is in the scientific literature, but this means that the chances that these results occurred by chance was 1 out of 20. That's all it means.

If a p value is at 0.68, which is either the NIS-LL score, that's a random chance of 1 out of 15. So I think that's what we're talking about. So I think, when it comes to a rare disease, it's a fatal disease. Are you willing to say that the efficacy has shown 1 out of 15?

Yes. It would be nice to have a second study

to confirm that and make it much more likely to be true. But when you have such an orphan disease, from a practical point of view, it's very difficult to pull that off.

DR. FOUNTAIN: So now I think we've now progressed onto really discussion of the points. So unless you have a very specific, factual question to ask specifically to Dr. Farkas about his presentation, just so we don't lose sight of any of this, before we move onto the specific issues in the discussion -- so Dr. Chaudhry, was your specific question to Dr. Farkas about his presentation, or is it a more general comment?

DR. CHAUDHRY: It's kind of specific, I hope. So this is coming back to what Dr. Clancy raised, and I still want to have somewhere this information before, at least, I'm satisfied one way or the other.

So there are two things that continue to be of some concern. One is, of course, this p value. And second is the difference in baseline between the two groups.

I know that Dr. Farkas made this sensitivity

analysis considering baseline disease severity. And that moved the .04 efficacy evaluable to 0.16. I'd like to see that same data to see whether, if you just take the efficacy evaluable patients and then did the baseline disease severity, that .04 becomes .06 or .08, I'm less convinced. But if it stays at .04 or even becomes better, I am more leaning towards this positive outcome because we all agree that liver transplant was a genuine reason to drop out. But that still doesn't take away the baseline disease severity difference.

So is it too much to ask to evaluate that? So I don't know whether you can do it in your head with statistics.

(Laughter.)

DR. CHAUDHRY: But it would be nice to have that information. And I don't want to lose my chance because I have a second follow-up question which is unrelated, if I may.

DR. FOUNTAIN: Sure. Why don't we ask Dr. Farkas to answer that first question?

DR. FARKAS: I'm actually a comment back already, so I was thinking about something else. But

if I could just address the meaning of a p value of, say, .05. And I guess -- I can just kind of mention briefly for a second about the ability of a p value to predict that the drug actually works. And I think the best way that I can explain this -- and certainly I'm not a statistician -- is that if there were a group of drugs that were tested, and you knew ahead of time that none of them were effective, some would have a p value of .05, if you knew that none were effective, you're guaranteed, if you test enough drugs that are not effective, to get a p value of .05.

The p value of .05 does not tell you anything about if the drug truly works outside of -- well, I'll say the Bayesian thing -- outside of the probability that the drug actually worked. We don't normally use Bayesian statistics, but if you knew that the drugs didn't work, you would get false positives. All your positives would be false positives.

So we just should try to think, really, of exactly what the p value is telling us and not telling us.

DR. FOUNTAIN: So your second question,

clarifying question?

DR. SHEFNER: He didn't answer the first question.

DR. CHAUDHRY: Yes. I don't think you answered the first question.

DR. FARKAS: Could you repeat it?

DR. CHAUDHRY: So I mean, on your page 4, or whatever, this slide 7, you nicely demonstrated sensitivity analyses considering baseline disease severity. And you did that analysis for NIS-LL. The p .07, the intention to treat, now becomes .16.

So that kind of takes away my first thing. Well, the p value is going in the wrong direction once you include the baseline disease severity. But now, I'm coming back to the efficacy evaluable patients, which is the point Dr. Clancy had raised and I had been concerned about. There, the p value is .04.

If you now do this analysis with the same sensitivity analysis, considering those baseline differences in severity of 2 points or more, would the NIS-LL move from .04 to a different direction? If it does, that really influences my decision.

DR. FARKAS: But I think it came up before, and we didn't do that analysis. I guess what I tried to do in my talk is kind of caution about the way that we do calculations. And there was kind of one little phrase.

Actually, the more calculations that you do, the more that -- even if they're just kind of slightly different, each one comes out a little bit different. And I think Dr. Preston did mention -- I mean, we're talking about actually fairly small differences in p values. Maybe that's the thing to concentrate on. And again, I tried to kind of briefly say this during my talk. And that is that it isn't like a p value of .04 means the drug works and a p value of .06 means it doesn't work.

So I could guess, perhaps, that if that calculation was done, I would have no idea. It would either be a little bit bigger than .16 or it would be a little bit smaller than .16. But again, with this multiple testing problem, you don't know how much faith to put in that.

The second thing is that, really, in the

sense of the amount of evidence that we have, a change in the p value of some small amount doesn't make a large difference.

DR. CHAUDHRY: But at the same time, you're using that argument to move the .07 to .16.

DR. FARKAS: Yes.

DR. CHAUDHRY: I mean, you can't have it both ways. If you're going to tell us -- if you do use the disease severity, I'm convinced that the intention to treat is a genuine excuse, that there are people -- I shouldn't say excuse, but a genuine reason for efficacy evaluable to be used. And if that's the case, I would very much like to know, even though the numbers are small, because you do show slide number 7 for a reason. I want to see a slide 7A or something that says, is it still .04 or has it moved to .2? Even though it's not even a sub-analysis, it just makes me think a little bit differently.

DR. FOUNTAIN: Could I summarize the discussion maybe, so we could move onto some of the other points? So your question is, you'd like to see analysis of the efficacy evaluable population either as

Dr. Farkas did it in the sensitivity analysis or as in the other analysis, as the sponsor did it. And Dr. Farkas doesn't have that analysis. He hasn't done it. And the response is that you don't think it would make that much difference. The sponsor did a sensitivity analysis, imputing the answer, and you don't have the other result from the evaluation.

Is that correct? Since that seems to be the focus of our discussion.

DR. LOMBARDO: Dr. Schwartz, do you want to come up to discuss that? We'll have Dr. Schwartz come up to address that.

DR. SCHWARTZ: So if there was a sensitivity analysis done in the original study report, a logistic regression that also adjusted, within the efficacy evaluable population, for baseline and other explanatory factors.

In that analysis, the significance also was greater than .05. There are some reasons why this is the case.

If I could have slide 84, please? So in slide 84, you'll notice that there is a differential

relationship with baseline between placebo and tafamidis.

So as you move from left to right in increasing severity, there's a decreasing response rate with placebo. However, the tafamidis rate seems to be relatively constant with respect to the baseline severity levels. There is some decrease at the very end.

We've done an additional analysis, looking at the slopes for those baseline adjustments, and it turns out there are two different slopes. So doing a single baseline adjustment in the logistic regression is not the best baseline adjustment for that test. However, if we look at the continuous change from baseline, NIS-LL, to month 18, and we put a baseline-by-treatment interaction in the model, it's not significant.

So the simple baseline adjustment that we included in that analysis retained significance, whether we look at either the intent-to-treat or the efficacy evaluable population.

DR. FOUNTAIN: So you do that also with the efficacy evaluable population?

DR. SCHWARTZ: Right.

DR. FOUNTAIN: These results are from the intent-to-treat population?

DR. SCHWARTZ: The upper left is the efficacy evaluable population. The three other displays were taken from the FDA's analysis and they're the intent to treat.

DR. FOUNTAIN: Dr. Farkas?

DR. FARKAS: Yes. I think that Dr. Chaudhry expressed confusion about what I was trying to say about the p values, and I didn't address that, I don't think.

We can have the most confidence in the pre-specified endpoint, as that was calculated. And there are two of them, so if you kind of average them today and say a .09, or something, or .08. Then I guess I tried to show that there's different sensitivity analyses that you could do to try to understand how that primary endpoint came about. And some of those will give you a bigger number and some a smaller number. And it's very difficult to know which one is a better number. Okay? And they're pretty symmetrical

around the original number that you got.

So I guess to be kind of perfectly clear -- I mean, I think that there is room for judgment, but still, the best kind of numerical answer is still the primary endpoint, is still the p value from the primary endpoint.

DR. FOUNTAIN: Thank you. Perhaps we should move onto some other discussion. Does anyone have any other clarifying questions before we have other discussion?

Dr. Bagiella, is it in regard to clarifying or just a more general discussion?

DR. BAGIELLA: No. I was wondering whether we can know from the company how was the study powered, what were the assumptions in the power analysis.

DR. FOUNTAIN: So let's actually make it a point to -- there are many, many things we could discuss, so let's make it a point maybe to follow to the questions to make sure we actually get to the ones we need to address. And that'll come up very quickly, so I think we can address that.

If we need to come back to some other

discussion, we can, so that all the panel members have an opportunity to ask their questions and participate.

Is there a direct comment in regard to that?

DR. UNGER: This is not exactly a clarifying question, but it's an important issue, though, a burning issue.

DR. FOUNTAIN: It won't be covered in the questions? That wouldn't be covered in the questions?

DR. UNGER: I think we should discuss it for a minute before the questions, if that's okay. We take confidence from multi-center studies, where most of the centers go the same direction. And we worry about studies where we have the predominance of support of efficacy from a single center. And this is essentially what we have here. The rest of the study tends to lean in the other direction, so it makes us nervous. De facto, this is more or less a single-center study, with 58 percent of the patients from Dr. Coelho's site.

We talked this morning a bit about the objectivity of the endpoints. And certainly, the Norfolk QOL is all subjective and the NIS-LL is objective, but it requires an operator to measure

things. So there are subjective elements there and, as such, they are susceptible to bias. And the way we get around that, we hope, is to have a double-blind study.

So my question really is for Dr. Coelho. I hadn't recognized that she was going to be here, but this is a golden opportunity. The question is about the blinding, because it's so critical for these endpoints.

My question is, with 58 percent of the patients at your site, I'm wondering if there are maybe subtle effects that the drug has, that are not recorded as adverse events, but subtle effects that would lead patients to be unblended, or -- I mean, as far as I remember, these are capsules. If you held both the capsule for the placebo and the drug in your hand, can you tell the difference between them? What would you say about those questions?

DR. LOMBARDO: So I guess, as Dr. Coelho is coming up, just to introduce that more generally, there was no evidence of unblinding, certainly, that we could determine in terms of GCP and all of the evidence that we found.

Specifically, as I had mentioned before, as we move from Study 005 to Study 006, the fact that the change across the tafamidis-tafamidis group and the placebo-tafamidis group was different, I think, also gives some overall confidence in the fact that there wasn't unblinding.

But to your specific question, Dr. Coelho?

DR. COELHO: So I have no reason to think that there was any sort of unblinding. The capsules looked exactly the same way. And I think the patients had lots of doubts during the course of the study if they were on drug or not. Even the dropout rate for liver transplant probably reflects the doubts the patients had during the first year of the trial.

DR. UNGER: I very much appreciate hearing that from you. Thank you.

DR. FOUNTAIN: So now, just to organize the rest of our discussion, we've really already been discussing it, so this might be more procedural. But just to make sure we get to all of the points and discuss the questions at hand, the first issue isn't really a voting issue. It's a discussion issue, which

is why I'm anxious to move to it, to make sure we reach all the points.

Please discuss the strengths and weaknesses of Study 005, including the effects of the following factors, on its ability to provide substantial evidence of effectiveness. Please discuss how regulatory flexibility might be applied with regard to these factors; of course, that's exactly what we've been discussing. But it might be useful to organize our discussion around some of these things. And I'll go through them first so you know what's coming.

First is the p value for the pre-specified co-primary endpoint, then the nominal p values for the individual components of the co-primary endpoint, the p value for the efficacy evaluable population, the lack of control for multiple testing analyses of secondary endpoints, results of secondary endpoints, baseline imbalances, and then disproportionate support of efficacy from site 1 in Portugal, as we were just discussing, with little to no efficacy support from the combination of remaining sites.

Now, if we can, in that context -- this might

be with regard to the ultimate p values. If you could, ask your question again.

DR. BAGIELLA: Can we know how the sample size was calculated and what are the assumptions in the sample size?

DR. LOMBARDO: Dr. Schwartz can take you through those estimates.

DR. SCHWARTZ: Can I see the other slide that shows the comparison?

So your initial assumptions for the sample size estimate was a 50 percent response in the treated group with a 20 percent response in the placebo group. This would provide a 90 percent power, .05 alpha.

There was an assumption of a 5 to 10 percent dropout rate. The actual dropout rate was about 20 percent, equally split in both treatment groups for liver transplant. With the other few patients that dropped out for other reasons, there was a total of 30 percent dropout.

So to do an initial assessment to see how badly underpowered this placed us, I did a simple analysis to see, with the actual observed effect size

and the actual sample size that occurred, what we would have needed. So in the ITT population, we had a 45 percent response rate and a 30 percent response rate in the placebo group. In the tafamidis group, that was a delta of 15 percent as opposed to the 30 percent assumed.

We would have needed 230 patients per group without any adjustments for dropout, compared to the 58 per group that we assumed earlier. If you gross up for a 5 to 10 percent in the original plan versus the actual 30 percent that we obtained, the discrepancy between the actual study size and the required study size in this situation is quite a bit different.

DR. FOUNTAIN: So to summarize -- or I guess we can comment as well. So it seems to me, ultimately, you were underpowered because of the increased number of dropouts from liver transplantation and a smaller treatment effect than you anticipated.

So I guess the argument would be that although the p value is small, if you had had a larger group with the same effect, it might have shown a difference.

Anymore discussion, particularly about the p value for the pre-specified co-primary endpoints?

Dr. Shefner?

DR. SHEFNER: I guess it's directly relevant to this, but it also is relevant to the standards that we're being asked to apply and I just want to state my understanding for validation ,which is that if we're being asked to approve a drug on the basis of a single trial, the p value of .05 is actually something we're hoping to see much smaller than.

We're hoping to see very robust p values on the primary endpoint. And so we're worrying about the other direction. But in fact, to follow the guidelines, which I actually think are reasonable, we should be looking for significantly more robust p values than .05.

Would that be a fair summary for our guidance?

DR. KATZ: Yes. I think, if you're talking about the one study plus confirmatory evidence, then, which I think we're talking about, whether it's subpart H or just a traditional clinical outcome, yes, I think

that's the point we've been trying to make, which is that, again, when you're only dealing with one study, you'd like to have the same amount of evidence or the same amount of confidence that the effect is drug-related, as you have with your two studies at .05, again traditionally.

So yes. And Dr. Farkas talked about the document that we have which lists the elements -- I think I mentioned the elements of when one study would be considered acceptable for that sort of approval. And, yes, one of the first things you read about is a lower p value than you typically would see with the two studies.

DR. FOUNTAIN: So the specific discussion is about the p value for the pre-specified co-primary endpoints, and the general consensus has been so far -- obviously, it doesn't meet 0.05. Is that right?

So the question is anything that mitigates that, or would change it, or other analyses, or other issues just for the co-primary-specified endpoints.

Dr. Luan, would you still like to make a comment from earlier or a question? I'm sorry. I

skipped over you earlier.

No? Dr. Oaklander?

DR. OAKLANDER: I've been wondering what the right time is to discuss the impact of neuropathology on the analysis. I'm not sure that this is the right time, but I'm not sure when the right time is.

DR. FOUNTAIN: You can discuss it now if you think it's relevant.

DR. OAKLANDER: I think we've spoken a lot about the flexibility that may be needed for an orphan drug, but I don't think we've adequately addressed the problems that come with the pathology of this kind of a disease. And I think that has a real bearing on the analysis as well. And the problem is that this whole methodology that we all use and rely on is designed mostly to look at acquired diseases.

But this is a genetic disease, where the pathology has been ongoing since birth. And yet, the symptoms of it develop only at the very end, falling off the cliff. And so while 18 months is a very long time for a clinical trial, it's actually a very short time in terms of the proportion of the disease course.

So I think we're struggling because the data are equivocal, and that's why we're spending so much time on how to slice and dice them.

But looked at from a pathological perspective, this whole design is not going to be optimal to capture what we really want to know about this drug. And the way to think about that is how would this drug be used if it were available? It would not be used the way it was used for this clinical trial.

If there were a potentially effective treatment, all of the family members who might be at risk for this would go out and get tested. And then people who are asymptomatic or pre-symptomatic go on this medication. And then the kind of analyses that, really, we would care about would be Kaplan-Meier type analyses, where does being on this medication for 10 years, for 20 years, delay or slow your onset to symptom or to death?

So I think that that is germane in the sense that we're trying to pull out some information -- it's not designed the way the drug would really be used

because of the length of the illness.

DR. FOUNTAIN: Dr. Marder, did you have a question or comment?

DR. MARDER: I do. My problem is that we're being asked to look at a flawed study for many different reasons. And the way the analyses have been performed, it's not clear what we're exactly going to be voting on, the ITT group or the other group.

In addition to that, we're being forced to make assumptions about what things might mean or what does it mean when you have populations that are different, different disease duration, where are they on the disease, line of the disease, and so on.

I just find it very confusing. You want to do something good, but on the other hand, you have to face the facts that the data just isn't there at this point. But it's because the study perhaps is flawed, poorly designed, underpowered. So I'm a little confused about that.

DR. FOUNTAIN: I would let you respond, if you like, or I could say, I guess while we're here, solve it?

DR. KATZ: Yes. I mean, you seem to have gone right to the end. But these are the questions we want you to grapple with and we want to hear what you have to say. I mean, that's your view. That's fine. We understand what you're saying. Yes. We need to hear it.

Just as long as this is live, the comment about the pathology, and that it would be used early if it were available, and that this design may not really have been appropriate for the setting, that of course may be true, but this is what we have. So I'm not sure what the conclusion is from your comments, even though they may be completely correct.

DR. OAKLANDER: I didn't mean -- I agree the study was done as best as it possibly could be done, so I wasn't intending to criticize it in that regard. But I'm saying I think that that should be as much a reason for flexibility as the fact that this is an orphan condition.

DR. KATZ: Again, I guess I'm just not sure how that -- and we're perfectly willing to follow this out. But I guess I don't understand how that would sort

of factor into our being flexible.

Are you saying that we should presume it works in those people who are asymptomatic, or we should make it available because it might work in those people and they're going to take it anyway? I'm just not sure how that translates into our being flexible. About what? I'm just not clear on that.

DR. OAKLANDER: My major point was that it's difficult to know about whether something is going to be helpful overall in a disease with a lifelong course, that has been damaging neurons for decades before the symptoms even appear.

So we're trying to make judgments from a trial that's done at a time when the horse is already out of the barn, to speak colloquially. And we really have no data and cannot have any data about what the efficacy might be if this were used for long periods of time in people who are pre-symptomatic.

So I think you're right. I'm not coming down on one side or the other in particular. I'm just saying that we're being asked to discuss about regulatory flexibility and other considerations. And I

think it's not just that it's an orphan disease that's grounds for other considerations, but the fact of a lifelong disease that we're trying to catch only at the very end.

DR. FOUNTAIN: So you're suggesting, for future reference, that for neurodegenerative diseases, that long-term studies longer than normally considered might be necessary or important to understand if the drug is effective? Does that summarize what you were implying? Dr. Bagiella? Dr. Rosenberg?

DR. ROSENBERG: I think the regulatory flexibility applies as much to the underlying science as to p values. And personally, it's hard to divide it up strictly question by question. I'm going to take the liberty of addressing two questions at once.

I think that the Study 005, whatever you call it, isn't robust. It's confirmatory because just the results are sensitive to how you cut the data. But they're pretty impressive. They apply to a wide variety. It's not just that it's a bunch of endpoints, but they're very different endpoints, subjective neurology, subjective neuro exam, objective nerve

conduction, quality of life, and even your weight.

I'm very impressed by how broad that effect is. And I'm impressed by many of the effect sizes. We talk a lot about p values, but just forget about the p values. These are big differences. I mostly work on Alzheimer's disease. I doubt that I will live long enough to see these effect sizes in Alzheimer's disease. These are impressive.

I do think the regulatory flexibility may have to do to some extent with the biomarker and the measures. We all know, in Alzheimer's, it's taken a ton of money and a ton of work just to establish how biomarkers are relating to the underlying disease. In an orphan disease, we will not have that. There are not enough patients. The resources are not likely to be applied. We have to work with less evidence.

I think the TTR biomarker is quite persuasive to me because it closely mimics the genetic models. I know nature didn't make a model, but still, we've got an unusual situation where we have a series of mutants. They all have the same chemical effect, roughly, and they all cause the same disease. We've even got a

mutant that protects and we've got a drug that seems to mimic the protective effect. I'm very impressed by that.

Now, you could drive a truck through that and say, "Well, you can't establish how well it reflects the underlying disease." It's true. What we want with a biomarker is to say there's a latent variable, which is the actual disease, the progression of the disease. And it's a little bit of a leap of faith to go from what I said to saying this reflects the underlying disease. I think the regulatory flexibility is, I don't think we're ever going to get the 10-year ADNI study in this disease to answer that question.

So once again, I'd say I think we've got a confirmatory level of evidence. Hold it like this, and look at the graphs, and you see pretty sizeable effects, but you see p values all over the place, suggest to me that there's a fair amount of variance in the measures, and we're not sure which measures are most sensitive to change, and we're not going to find out. Once again, in Alzheimer's, we've spent millions of dollars answering those questions. It takes many

years.

But I think the biomarker is pretty persuasive and the idea, to me, I think meets whatever you call it, subpart H because I think there's substantial evidence for the biomarker. I mean, it's very clear they affected the biomarker. And I think the biomarker is reasonably likely -- do you follow me -- based on the genetic models.

It says it does not allow for approval based on weak evidence of effect on clinical endpoint. I don't find the evidence weak. That's my personal opinion. It's not as robust as it could be, but it's not weak evidence. And once again, let me repeat it's because of the variety of measures. And the last is, there's got to be a post-approval study.

I'm sorry to go all over the place, but I think it's hard to just answer one question at a time.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: Yes. I'd like to throw my two cents in about the p values. I was just imagining that the sponsors did a huge study. They did 500 patients in each side, the placebo side and the active drug

side. And when all was said in done, they could show, with a p value of .0001, that there was 1 percent better response rate in the drug compared to the placebo group. And we'd be very satisfied. This is significant because the p value is so small. But would we really care about such a small chunk of change in a disease that's so progressively relentless?

It seems to me that, for something that's measured over 10 or 15 years, to be able to find, I think, a clear signal in 12 months to 18 months, is meaningful. And again, if you get back to the fact that this is a disease [sic] that you want the patient to take every day, every day, every day for a month or a year, that is the patient population I'm interested in, not the ones that fall by the wayside. We're looking at a chronic disease.

So anyhow, I'm less focused on the equivocal p value than what seems to be a consistent signal in the primary, and secondary, and some of these objective things. That tells me there's some help to offer these patients from this drug.

DR. FOUNTAIN: Does someone have a direct

response to that or onto another question?

DR. SHEFNER: Basically, a response to both together, dealing with the size of the point estimate rather than the p value, I just think it's important to say that the point estimate in a study this size is almost meaningless. Basically, all it tells you is that you have a 95 percent chance of being between two very large numbers, which go from close to nothing or negative in some values to very large.

So if those point estimates actually were reliable and indicated something, then they would be incredibly valid. But there is example, after example, after example of small studies in neurodegenerative disease with humongous point estimates that, on repeat study, go away entirely. And they include ones where many measures change together.

DR. FOUNTAIN: That would seem to be the crux of the problem, two views. Dr. Kramer?

DR. KRAMER: I don't have a question anymore. It was already kind of asked and answered.

DR. FOUNTAIN: Dr. Gooch?

DR. GOOCH: Yes. I'd like to make a couple

of points, I think. So the first point, I think I just want to echo what's been said about the evaluable efficacy population in this study and the fact that the liver transplantation situation creates a fairly unique circumstance here. And I think it's important to look very carefully, and it's on our list. And I'm going to jump around a bit, too. But I do believe the efficacy evaluable population in this circumstance has particular relevance to the significance of the study.

I want to talk about surrogate endpoints because that's come up. And I'm, in large part, a neuropathy specialist, as are a number of the neurologists on the panel. And I want to talk about two specific things that, in looking at some of the surrogate markers, came out as being quite significant in this study.

One is the effect on small fiber function, so this was looked at, at the sigma 3 subscore and had a high level of significance. This is important for two reasons.

One is that this is really the first population of neurofibers to be affected in this

particular condition, so in a sense, this is in essence a canary in the coal mine in regards to this particular kind of neuropathy.

It is, as has been alluded to, a brief duration to test for a long-term disease. So to see significance in the earliest part or in the part of the nervous system where you would see the earliest effects of the disease over this brief window of time does carry some special importance.

I think we have to think about that. It's also important to remember that most of these patients were ambulatory patients when they came in, so these are not the most severely affected patients.

So we're looking at that point of the curve where small fiber dysfunction, I think, has special relevance. And small fiber dysfunction, as measured by quantitative sensory testing, has been correlated quite clearly in diabetic neuropathy with significant pathology and morbidity. The development of pressure ulcers is one of them. Neuropathic pain is another. So it has direct clinical relevance, which is applicable to subpart H.

The second thing I want to emphasize, which has already been mentioned early on but is of great importance to the patients is the effect on strength, so particularly distal leg strength.

So this is another classic feature of distal symmetric neuropathy. And when patients begin to lose significant distal leg strength, it dramatically affects their ambulatory ability. It affects their mobility. It puts them at increased risk for all kinds of injuries.

In this study, when we look at the distal muscles, especially in the subanalysis that was done, we see that there is quite robust p values, looking at those distal muscles in the legs in this particular study. And that, for the patients, is very important. So I think, as we begin to dissect it out -- and again, these are surrogate markers; they're not the payment endpoints -- taking together the fact that if we look at the efficacy evaluable population, and then we look at these very important, very relevant endpoints for patients with neuropathy and with particular application to this individual neuropathy, that it

makes a relatively compelling case, even given the weaknesses of the study, that this is an effective drug.

DR. FOUNTAIN: Is it directly related to that, or in response to that, or another question?

Ms. House? I'm sorry. You want to respond to that first, Dr. Katz and then Ms. House?

DR. KATZ: Again, just to remind folks of some of the points that Dr. Farkas had made earlier about this small fiber test -- slide 13, small nerve fiber test -- a couple things. First of all, it does have a small nominal p value, but again, in the background of many, many things being tested in no prospective order of testing, it's difficult to know what that p value means, again, in the setting of the lack of significance on the primary endpoints.

I know we've been talking about evaluable patients -- but maybe if you have the slides at your desk -- that point, the 18-month point, where you see this nominal significance, patients continued to get worse on that, even patients who were on placebo before who now in Study 006 are getting the drug, and now

they're getting worse.

That point, as Ron pointed out, could have been a chance finding. It seems to be, if you tried to draw the curve, connecting the dots. That seems to be perhaps out of line. And again, given the multiple, multiple comparisons, the meaning of that particular comparison and the meaning of a nominal p value of .05 at that particular point, I just raise again for people to consider.

Obviously, people can conclude what they want about that.

DR. FOUNTAIN: If it was random, though, wouldn't you expect it to have some variance around that, rather than just not follow the same trajectory?

DR. KATZ: Yes. But it's just potentially anomalous, again, given the multiple comparisons.

DR. GOOCH: May I respond? Yes. So I wanted to actually address this slide. I'm glad you brought it up. So in this particular circumstance, in some of the work that we have done and others have done, in terms of neuroprotective drugs and the way that they often work, we will often see an early effect that is

more dramatic and that creates a separation of the curves between the untreated population and the treated population, and then the patients begin to progress further. And our theory, my theory about that, is that there are some nerves, in this case small fibers, that are, if you will, barely alive, barely functioning, and that the treatment basically salvages them and enables an ordinary repair processes that the peripheral nerves have to kick in and bring them back into function, which gives the patients an early bump. Then after that, the disease process continues at some level and further progression occurs, although there may be further benefits.

However, this does not mean the drug is of no benefit. It actually is kind of like the horse getting out of the gate, and getting two lengths on the rest of the horses, and maintaining it going forward. There still is benefit.

So to me, this is actually a pattern that suggests, actually, in my mind, reinforces this particular paradigm of pathophysiologic benefit. But it is true that the separation is not getting wider and

wider.

DR. FOUNTAIN: Unless we have a direct response to that, maybe we should take the opportunity to take a break and then follow up with the other questions. Quick response to that?

DR. SHEFNER: Really quick, just two points. One is that if you look at the sensory component of the NIS, both in the Porto cohort and in everybody else, it's changing less than everything else. So these are two inconsistent observations. And I guess I'll stop at that.

DR. FOUNTAIN: Ms. House, would it be all right with you if we broke first and then have your comment afterwards? Thank you. And I realize there are also others waiting as well.

So right now, let's take a break for 15 minutes. It's 3:10, so let's be back at 3:25. And please remember not to discuss the topic of the meeting outside the meeting.

(Whereupon, a recess was taken.)

DR. FOUNTAIN: Welcome back to the meeting, to the voting portion of the meeting. And we'll resume

where we left off. I think we were up to Ms. House's question or comment.

MS. HOUSE: Hi. Thank you. There has been a lot of discussion about p values, and I'm not going to talk about that because that's not my place as a patient representative. I wanted just to make some comments about some of the things the patients said, some of the things that I've heard around the table.

First thing I wanted to note was, one of the patients, when he spoke, said that if we decide to go ahead and approve today, that we will help a lot of people, that no one is going to be hurt. And I think that's something that I'd like us to think about real carefully because nobody's talking about the safety or any risks here, because I don't think there are any. From the AEs that I've read, the serious AEs, all of that, they aren't related to the drug. Or if they are, they're pretty minor and can be managed.

So if there isn't a risk, then we need to be really focusing on benefit, which we are. And I think, again, as has been talked about, all of the trends seem to be in the direction of there is a good chance that

there's a benefit.

So that leaves us at, how do we approve it if that's where we want to go? And we're not talking about traditional approval because I think the sponsor has agreed that's not the direction we're going. We're looking at an accelerated approval with a study attached. So we're not giving broad-label approval to use it with anybody. We're trying to make it available to patients who need it now.

Like the FDA suggested, there's always a chance of expanded access for these patients. But you heard one of the patients say doctors aren't interested in it. Speaking as a patient with a rare disease, I know that's true. A lot of doctors are going to step back and say, "I see what you're saying, but it's too much work for me."

So if we say it's safe enough and there's enough suggestion that there's a benefit to go with expanded access, why don't we just say, "Let's go ahead, and give it accelerated approval, and come up with a good study design," because we're having the same effect that we'd want to have, giving it to the

patients, but we're not facing these insurmountable hurdles. And expanded access can be an insurmountable hurdle. So that's all I wanted to say.

DR. FOUNTAIN: Just as a minor point of clarification, we're not really voting for approval. We're just voting on the questions to give our opinions about the issues at hand.

DR. KATZ: Can I just make a comment? I appreciate your comments very much. I know there's been a lot of talk here at the table about p values, and it's a very arcane discussion and analyses. And it seems as if the patients are secondary in these discussions.

I think our obligation is to make sure that only drugs that work are approved. And I think everybody would agree it doesn't do anybody any good to put drugs out there that don't work. So how to determine whether drugs work could be complicated and it's obviously complicated in this case, but that's at least our minimal obligation, I think.

I just don't want people to think that the patients aren't critical. Everything we're talking

about ultimately is about the patients. We're just trying to figure out whether the drug works. It doesn't have to work a lot. We just have to convince ourselves that it works. And the only way to get there is to talk about p values and analyses. And so I know there's a perception that the patients aren't critical. Everything we do here is about the patients. It's just a question of how do we get there.

DR. FOUNTAIN: Yes?

DR. ENSRUD: Hi. Erik Ensrud. I had a question for Dr. Grogan or someone from marketing in Pfizer. We've talked about how few patients have this disease, which of course doesn't matter for the patients and families who have it.

It's difficult to identify these patients. There's been a lot of delay, it sounds like, in some of the families who spoke today about diagnosis. And there's been a pretty vigorous marketing effort from Pfizer about identifying people with idiopathic peripheral neuropathy and for education as to whether they might be candidates to being tested for TTR.

I wanted to ask, it seems like there's

somewhat of a precedent that's been set for rare diseases in terms of Genzyme, that they will now pay for the testing for acid maltase disease and Pompe disease. Because the cost of a test -- and it's my understanding that the testing for TTR, the genetic testing, is about $500. Actually, the modern-day American healthcare system can actually be a significant hurdle. And I wanted to ask if there's any plan on the part of Pfizer, similar to Genzyme, to pick up the cost of that testing.

DR. LOMBARDO: Thank you. So I'm Dr. Lombardo. I'll take that question. And certainly, as you've mentioned, with TTR-FAP as with other rare diseases, it's very underrecognized, and as has been mentioned, underdiagnosed. Obviously, when a drug is approved, it affords us an ability to help with patient education and with some types of disease awareness as well.

The actual activities that we would be doing in the post-approval setting obviously haven't been committed to yet, but we certainly are committed to this disease, to continue working in this area, and

certainly working with patients and physicians with TTR-FAP.

DR. FOUNTAIN: Dr. Logigian, did you actually have a question from earlier? I'm not sure if you still have the question.

DR. LOGIGIAN: Yes. Maybe I'll just sort of ask the question at this point. There have been a couple of remarks, I think, headed in this unvalidated surrogate direction, one using the assay and then one for more small fiber function.

So at this point, if we think the weight of the evidence is not strong enough in terms of p values, and in terms of validation, more than one site, and that sort of thing, to approve based on one study with confirmatory evidence, then one then turns to the possibility of the surrogate, an unvalidated surrogate pathway?

First of all, correct?

DR. FOUNTAIN: Dr. Katz?

DR. KATZ: Again, you certainly can consider the surrogate subpart H pathway, but you still have to have substantial evidence of effectiveness for the

effect on the surrogate. And that still, I think, puts you in the realm of one study plus confirmatory evidence standard for demonstrating that there is that effect on the surrogate. Then you could talk about, is it reasonably likely to predict the clinical benefit you care about. But we have to find that there's substantial evidence of effectiveness for the surrogate.

So even if you're talking about subpart E, we still have to deal with the question of how robust -- is the evidence for the effect on the surrogate robust enough that the one study plus confirmatory evidence standard applies?

You could find that it does, but we have to make that finding to move forward.

DR. LOGIGIAN: So of the five -- using the changes from baseline to 18 months, of the five various tests, we have the NIS, the QOL, small fiber function, large nerve fiber function, and the modified BMI. And of those, the strongest ones -- and I guess you could add maybe the assay. I'm on page 39, slide 77 from the sponsor.

Actually, these are baseline. I think there's a summary.

(Pause.)

DR. LOGIGIAN: I guess one could use those, but there are p values, I know, and I've lost the original page here. But the p values are the strongest for BMI muscle, the NIS, particularly muscle weakness and the small fiber function. So I guess my question is, what does one have to show to prove that one of those would be eligible for this pathway?

One would have to have two things, as I understand it. The surrogate data has to be substantial and also that the effect on the surrogate is reasonably likely to predict a clinical benefit.

So one could make that argument certainly for muscle strength and potentially for small fiber function. And then the question that I have in my mind is, is that data substantial? The p value for the muscle weakness, I think, is .01 and .005, I think, for small fiber. Yes.

Does that constitute substantial evidence, or is that surrogate data substantial? Does one need two

pieces of information, for example, for muscle strength or the same for small fiber?

DR. FOUNTAIN: Would you like to respond to that or is that the nature of what you're asking us?

DR. LOGIGIAN: Yes. I'm asking.

DR. FOUNTAIN: Yes. Please respond.

DR. KATZ: Again, the determination that, for a particular outcome, there is substantial evidence of effectiveness is a judgment. There are the usual sorts of standards that we apply. We talked about two studies with a .05 or one study with usually a lower .05, plus something called confirmatory evidence, which is also something that is a judgment.

Again, I would only point out, for the ones that have been discussed, which we just mentioned, there is the multiplicity question, the question of the muscle weakness at .01, but it wasn't a primary -- it's a component of one of the primary outcomes. It's one of many things, similarly with the .005 for the small fiber function.

So you can recommend that, of course, in your judgment, in your view, there is substantial evidence

of effectiveness for an effect on muscle weakness or the small fiber. But again, I would just raise the point that when you're talking about a single-study standard for a particular outcome, whatever your outcome that you choose is, we would normally expect that to be quite robust, more robust than either of two study approvals.

So you would have to decide whether you thought that met that standard. But the standard for one study, substantial evidence, is a study that's very robust, whether it's on the clinical outcome or the proposed surrogate, typically.

DR. FOUNTAIN: Dr. Mielke, did you have a comment or question?

DR. MIELKE: Yes. I guess more of a comment. I mean, as we've been talking a lot about the p values, and what's significant, or not, and flexibility. I think one thing that's been in the back of my mind, that I'm struggling with a little bit, is, we're focusing on the endpoints. But as was mentioned a little bit earlier, when you think about the risk-benefit ratio and adverse effects, I guess I'd be a

little bit more concerned about the very highly significant p values if there were a lot more adverse events.

Since there aren't really a whole lot -- I mean, certainly there are some risks. There are risks with any kind of drug and this hasn't been conducted long term in a lot of people, so there's potential for risks. But that gives me or pushes me a little bit more in the direction where I'm not quite as concerned about the lack of very highly significant p values. I don't know if that's something that we should consider or not, but that's kind of been in the back of my mind a little bit.

DR. FOUNTAIN: Dr. Shefner?

DR. SHEFNER: I just wanted to caution once again about the equivalent version of that slide that took away that one site, where the pattern was not at all seen in every other site. And I think that concerns me significantly.

DR. FOUNTAIN: Can I ask a point of clarification from the sponsor? I think I heard you say that the total exposure of the drug was 127. But

yet, there were 125 in Study 505?

DR. GROGAN: Throughout the whole development program for FAP, the total number of patients exposed is 127, so that includes the 65 patients in the tafamidis group from 005, the patients that were previously on placebo that went on tafamidis in 006, and then the patients that were exposed in the 1-A-201 study.

So all the total number of patients ever exposed to tafamidis is 127.

DR. FOUNTAIN: So not all of the placebo patients went on tafamidis in 006?

DR. GROGAN: Of the 91 patients who completed the trial, 85 went in, so very few did not roll over into that trial.

DR. FOUNTAIN: So I guess my comment is, that's still a pretty small N in terms of safety.

Yes, Dr. Farkas? Did you want to make a comment, Doctor?

DR. JILLAPALLI: During the last hour, Dr. Shefner asked for site 1 versus an all-of-the-sites-combined analysis. We have some p values if some of

you may prefer that.

These are all ITT analyses. At month 18, NIS-LL response rate at site 1 was 0.0044. At all of the sites, it was 0.5723. And for the NIS-LL change from baseline, at site 1 it was 0.0090. And at all of the sites combined, it was 0.7347.

For the TQOL change from baseline, at month 18 at site 1, it was 0.133 and, at all of the sites, 0.865. Large fiber change from baseline, month 18, at site 1 was 0.0419 and, at all of the sites, was 0.8364.

DR. FOUNTAIN: Dr. Chaudhry, did you have a comment or question?

DR. CHAUDHRY: Yes. So this is my first time in such a hearing, and I was very touched by the emotionally powerful testimony by family, and friends, and individual patients, and thank them for coming.

I don't know how we're supposed to incorporate that into this, but one thing I did learn in my own experience as well is the fact that small fiber neuropathy, painful symptoms, and autonomic symptoms are pretty much part of this disease.

As this analysis was done, I mean, there are

two things I'm looking for, subjective improvement and an objective improvement. In this case, the subjectivity is by quality of life, which didn't show, and objectivity is by the testing, the NIS-LL, which also didn't show in intention to treat any change.

I just wonder why -- I mean, is there any way we can have -- from the quality of life, find out whether there was a pain scale measured or if patients complained? I mean, we heard today that patients are on narcotics and such. All the autonomic testing, which in this case is listed for some reason under large fiber and small fiber.

Was that in any which way changing? Because those are two main components of this disease as functionally subjective. And I know, through the progressive process, the weakness comes in as well.

So I guess a direct question to the sponsor is, why wasn't a visual analog scale or any pain measurement given? In general, my experience is, subjectively, patients report much more improvement than objectivity. In this case, we don't see that. Perhaps it's in that TQOL, and I didn't see that in

detail. Was that done? And did the heart rate variability with deep respiration change through this whole study?

DR. FOUNTAIN: So if we could ask you to respond if you have any data about that, what about the quality of life contains a pain scale and again, show whether or not heart rate variability changed?

DR. GROGAN: Sure. Yes. I can show you the components of the quality of life. Approximately 30 percent of the patients enrolled in the trial across the treatment groups had pain as a component of their neuropathy. So although it's definitely a component, it may not be quite as common as in, say, diabetic neuropathy.

If I could show slide E188, please. So these are the individual domains for the total quality of life score. Again, remember that this study was not powered to show differences between these individual domains. Symptoms scored there, you can see numerical differences favoring tafamidis, small fiber function, and in particular the large fiber function, which does match with what we saw with the NIS-LL, muscle weakness

scale.

If I could have the adverse advent profile from the core deck, please?

So I went through safety fairly quickly in the interest of time. Slide 123, please? And we highlighted at least those adverse events that were reported more frequently in those patients on tafamidis. We did not do a visual analog scale in this trial, but the adverse event profile is listed there. And you do see that at least paresthesias and neuralgias were reported more frequently in patients on placebo.

Then can I have the heart rate response to deep breathing, please? The one measure of specific measure of autonomic function, the heart rate response to deep breathing, as Dr. Freeman noted, was assessed. And this is the normal deviate values for that. And you can see that there is virtually no change in the heart rate response to deep breathing in patients on tafamidis and a worsening in patients on placebo.

Higher normal deviate scores show a worsening. If we looked at the raw values, the beats

per minute, you'd see a decrease in the patients on placebo.

DR. CHAUDHRY: Can I have a follow-up on that?

DR. FOUNTAIN: Okay.

DR. CHAUDHRY: Is there a plausible explanation why the large fiber function appears to improve more? Is this drug not able to or is the deposits of amyloid -- you're not able to penetrate smaller fibers or something? Because I'm looking at, is strength improving, large fiber function improving, but not particularly at least the p values. I know the trends look in the direction of the drug.

DR. FOUNTAIN: So maybe in the interests of time, we could have a yes or no answer about whether or not you have an explanation.

DR. GROGAN: I don't think that's an accurate assessment, actually. I think we have similar effects on both small and large fiber function.

DR. FOUNTAIN: Thank you.

We do need to move onto the questions, so I'd like to summarize the discussion points that we

considered before, which we talked about in various considerations. The first one was the p value for the pre-specified co-primary endpoints. I think we talked about that in quite some detail.

I'm not suggesting we reached a consensus opinion, but I think the issue is whether or not those are significant. And the general answer was no, that some may think differently. The nominal p values for the individual components of the co-primary endpoints, which I think follows directly on A, having similar issues; the p values for efficacy evaluable population. So we had a separate discussion about the efficacy evaluable population and the p values, and looked at some other data that wasn't presented before.

DR. PRESTON: Could we discuss that? That was one of my questions from this morning that was tabled until this afternoon.

DR. FOUNTAIN: Yes. So if you have a specific issue or question --

DR. PRESTON: My specific issue is, I really would like to hear from the statisticians from the FDA and the statisticians from the sponsor. And that is,

the intention to treat clearly did not show that this treatment, with confidence, actually works. But it's a very unusual thing because people were taken out because of this liver transplant. And this is a very unique situation where, when someone's offered a liver, they're likely not going to say no.

When you look at the efficacy evaluable p values and the robustness, it's actually pretty good or at least much more impressive. But I'm not used to seeing this, but I think this is a distinctly unusual situation because, normally, I would stick to the intention to treat, period. But this is so unusual. It's not a patient who's deciding by themselves to go out. It's almost like they have a gun to their head about, do you want this liver transplant or not? Here's your one opportunity. They're going to jump at it and take it. And the question is, because of that, should we put more emphasis on the efficacy evaluable than we normally would?

DR. FOUNTAIN: So I think that's a question that's kind of asked to us in the nature of these discussions. So if you have a specific question about

some clarifying data or analysis, unless someone would specifically like to respond, I think the question before us is, is that acceptable? I think that's the nature of your question.

DR. KATZ: I would just say, I don't think it's a statistical question, actually. I think it's a question of whether or not you think it's appropriate to essentially ignore the primary analysis because it's not appropriate in this setting and that the efficacy evaluable population is the more appropriate population to analyze.

I don't know. Call it a clinical judgment or whatever. I don't think it's a statistical question strictly. It's a judgment thing, I think.

DR. FOUNTAIN: Dr. Luan?

DR. LUAN: Just to continue Dr. Katz's discussion, I think we have brought this up, the efficacy evaluable population, several times during the discussion. I just want to add a few of my quick comments.

I think in principle, we all know that the primary efficacy analysis should be based on ITT. And

the purpose of the analysis based on the efficacy evaluable population is just to assess if the primary efficacy analysis on ITT -- whether or not it's robust.

The p values from the efficacy evaluable population should not be interpreted as evidence for efficacy. But we all know in this particular case, it's often judged rare disease, super rare disease. How much flexibility do we want to exercise here? But before we reach a conclusion, I want to bring up two points that maybe the committee can consider.

The first is, this is a very small trial. It's 125 patients for the ITT. And out of the 125 patients, 26 patients went to a liver transplant. That's about 20 percent of the ITT population. Whether or not we threw away all the 20 percent population, 20 percent of the patients, whether or not it's appropriate, is worth consideration.

The second point is, I think, this morning, the sponsors showed us slides which compared the baseline characteristics of the patient that had a liver transplant and a patient who did not have the liver transplant. I think, in that slide, we see that

the patient, actually, who went through the liver transplant seemed to have the most severe disease. And for the patient who has the most rare disease, based on the data, they are more likely to become a non-responder.

So I think, if we throw away all the patients that had a liver transplant and do the analysis, I think the results will be biased and will favor the drug. Thank you.

DR. FOUNTAIN: Anymore discussion? Personally, I think like you, Dr. Preston, that it's a very special circumstance.

Anymore other discussions about that? Yes?

DR. JILLAPALLI: I just want to add one more thing regarding the efficacy evaluable population. On the one hand, the dropouts due to adverse events were low and even, and the dropouts due to liver transplant were more fairly even. So that just provides us some limited reassurance about the bias being introduced.

But there is one important thing, as Dr. Luan pointed out, is that the number of people that dropped out were not trivial. They were 20 percent. And that

introduces all sorts of biases in a sum that we can find difficult to quantify. And there will be other biases that might be introduced that we may not even be aware of, that might be influencing one treatment group over the other.

DR. FOUNTAIN: Thank you. So we talked about lack of control for multiple testing and, now, secondary endpoints, results of secondary endpoints, which I think we talked about, proposed even some surrogate markers, baseline imbalances, which I think were covered very well, and disproportionate support of efficacy from site 1 in Portugal, with little or no efficacy support from or in combination of the remaining sites, which I think we also heard a detailed analysis of and clarified the issues on, regardless of which side of the coin you agree with.

So now, let's turn to the voting questions. For approval based on a single study plus confirmatory evidence, this study is expected to be particularly robust. Note, however, that not all characteristics that might make a study particularly robust need to be present.

So we'll vote on this question. In the context of the above discussion, are the findings of Study 005 sufficiently robust to provide substantial evidence of efficacy, similar to that usually provided by two supportive studies for a clinical endpoint?

So we'll begin voting, and during voting, your microphone will flash. And you can press the button as many times as you want, but the last time you press it, it will register your vote. So begin voting now.

(Voting.)

DR. JOHNSON: I will now read the vote into the record. We have 4 yeses, 13 nos, and zero abstentions.

DR. FOUNTAIN: Now, we'll go around the room and ask you to state your vote. And if you wish, you can provide an explanation. Before you begin, please state your name. And why don't we start with, I guess, Dr. Cohen?

DR. COHEN: So this is a weird situation for me because I'm always consumer patient advocate. What I had trouble with was the one study, the study in

Portugal versus the findings with the other studies. And kind of in the sense of being a clinician, taking care of these patients, those data didn't jive really with my clinical experience. So, yes, I would like to have this drug available in a select group of patients. I think it's important. But this study, as Dr. Marder said, was really flawed.

DR. SHEFNER: So this is Jeremy Shefner. I voted no, primarily for two reasons, first the finding that the primary efficacy signal was in one site and not replicated in an almost equal sample of the other sites combined, and second, just in comparing this dataset in its entirety to my experience of other similarly-sized studies that didn't have confirmatory evidence when larger studies were performed.

DR. CHAUDHRY: This is Vinay Chaudhry. I voted no for pretty much the same reasons as the other two have just said.

DR. PRESTON: This is David Preston. I voted no as well, with a heavy heart because I realize that this drug probably has little toxicity, but I think, looking at the question, there really is no evidence

for efficacy and certainly not robust by any stretch of the imagination. Unfortunately, as noted earlier, the study was really underpowered. And really, we can't draw any conclusions.

DR. VERMA: This is Dr. Verma. I voted no. But I'm convinced the directional effect is there, but the magnitude of effect is not there to vote yes. So given the criteria, I think it's no.

DR. OAKLANDER: This is Anne Louise Oaklander. I voted no with difficulty, but this study is not just flawed in one regard, but it's flawed in virtually every single way. It has virtually every single kind of flaw that it could have.

So I think we really have to draw the line between wishful thinking and looking at the data. Furthermore, I think I listened with caution to the statements that this drug is safe, because I don't think we really know if this drug is safe or not. The number of patients studied and the time that the drug was taken for, as compared to the time that it would be used for in clinical practice is so small that I don't feel confident that we have enough data to judge

safety, either.

DR. BAGIELLA: Emilia Bagiella. I voted no. And as the others said, I don't think that a single study provides sufficient evidence of efficacy of the drug.

DR. MARDER: Ellen Marder. I voted no for all the same reasons.

MS. HOUSE: Tiffany House, and I voted yes. I understood all the concerns that were raised, but I think, with a degenerative disease like this, where you are not going to get better, and it's fast, it's 10 to 15 years, that any slowing is evidence that it's working. And I think that all of the trends were enough for me to say that it was effective.

DR. FRANK: Samuel Frank. I voted yes, but it would be a very weak yes. I think if you look at the primary outcome, the co-primary endpoints in the efficacy evaluable, they did reach a statistical significance, and I think we have to start with that. And all of the trends in the secondary outcome measures were in the right direction.

I say yes with hesitation because of the

issues that we've already discussed, but I think that it's important enough that -- the other thing I wanted to say is Dr. Oaklander's comment about this being a snapshot of a disease, which is very true. We're looking at 12 months, 18 months, up to 30 months of a disease that lasts 15 years. So to even get a suggestion of a clinical response, I think, is actually impressive for such a short time.

DR. OAKLANDER: It lasts your whole life.

DR. FRANK: It lasts your whole life. Yes. You're born with it.

DR. OAKLANDER: It may not become symptomatic until the end.

DR. FRANK: Right.

DR. OAKLANDER: The nerve degeneration has been going on for 40 years.

DR. FRANK: To see a signal, I think, was enough clinical evidence for me to say yes.

DR. FOUNTAIN: Nathan Fountain. I voted no because the emphasis on this question is for clinical endpoints and I believe that's true for the primary endpoints, although I believe, for the biomarkers and

other issues, there may be other evidence. But in this specific question and context, I voted no.

DR. CLANCY: Robert Clancy. I voted yes. We talked about flexibility a lot. And it seems to me that the place where we can apply this again is in defining who the populations are we're interested in.

The reality of this disease is that people are going to get liver transplants. And if you do two more studies or a longer study, there's still going to be a lot of dropout from liver transplants. That's not cherry-picking the population. It's not like picking the good cases that seemed to work. It's just the way the cards fall for these people.

Again, for a chronic disease that's going to be progressing over 10, 15, 20 years, I do want to know, if you take the medication for 18 months, does it give you an advantage over the placebo? Then the primary clinical outcomes are significant, which allows me to say, "Well, now, I have a validation to start looking at secondary outcomes." And they're at least consistently favorable.

So I thought overall, on a dark night, even a

small sliver of the moon is better than no moon at all, so I voted yes.

DR. MIELKE: Michelle Mielke. I voted no, based on the evidence of one trial and the not extremely highly significant p values.

DR. LOGIGIAN: Eric Logigian. I voted no. This is a devastating disease. It's a terrible axonal neuropathy. I don't think the study was flawed so much as just a very challenging problem. And in some ways, I'm amazed. I've seen some of these patients completely paralyzed from the knee down. I'm amazed that we saw a signal at all.

The problem was that even if you use the sample without the liver transplants, your p values were not quite as robust. And then we had the nagging problem that most of the benefit was really from one site.

DR. GOOCH: Clifton Gooch. I voted yes for some of the same reasons that have been elucidated. Number one, I agree strongly with the statement that's been discussed, that this is an unusual circumstance and the validity of looking at the evaluable endpoint

population is quite relevant here, given the whole issue of liver transplantation.

So really, there are two parts to this. One is, do we have the reproducibility? And one is, do we have the core data? I think, with the evaluable efficacy, we do have significance, which is the 005 study. With the 006 study, of which the data was presented, we didn't talk too much about that. With the crossover from placebo to open label, I thought there were further signals of significance, which was sufficient for me in this particular unique circumstances to vote yes. And I usually also go with intent to treat, but here I believe it's appropriate to take this different approach.

DR. ROSENBERG: I'm Paul Rosenberg. I voted no because I don't think it was robust results for the clinical endpoints.

DR. ENSRUD: Erik Ensrud. I voted no. We have a series of questions here that are set at different bars. This question is a very high bar, and I didn't feel the study, although I agree with Eric Logigian that I don't see it as a flawed study, I

actually think it's a commendable study, but it didn't meet this particular question.

DR. FOUNTAIN: That's all of our voting members. Part B now is just a perfect follow-up to your comments.

In the context of the above discussion, are the findings of Study 005 sufficiently robust to provide substantial evidence of efficacy, similar to that usually provided by two supportive studies for a biomarker rather than a clinical endpoint, that is reasonably likely to predict a clinical benefit?

So we will begin voting now in exactly the same manner.

DR. COHEN: Dr. Katz, can you just clarify biomarker?

DR. KATZ: Clarify biomarker? Yes. Again, maybe it was an inelegant word. We are looking for surrogate. So again, usually it's some sort of a lab test or something like that. It can be a clinical endpoint that you feel is not the real clinical endpoint you care about, but one that predicts a clinical endpoint that you care about.

(Voting.)

DR. FOUNTAIN: So has everyone voted? Yes, no, or abstain.

[Voting.]

DR. JOHNSON: I will now read the vote into the record. We have 13 yeses and 4 nos.

DR. FOUNTAIN: Let's start on this side with Dr. Ensrud this time.

DR. ENSRUD: I'm Erik Ensrud. I voted yes. I felt, based on the wording of this question, the sigma 3 sum score, including the small fiber and the TTR stabilization, met the query.

DR. ROSENBERG: I'm Paul Rosenberg. I voted yes, same reason as he did.

DR. GOOCH: Clifton Gooch. I voted yes, also not only because of the significance of the small fiber QST results, but also because of the significance when the muscle strength testing was assessed, which I think both are very relevant measures clinically to patients with this particular form of neuropathy.

DR. LOGIGIAN: Erik Logigian, weak yes for muscle strength.

DR. MIELKE: Michelle Mielke. Weak yes for muscle strength as well. I think there are some weaknesses in the main positivity at one site that worries me a little bit, but I think the positives certainly outweigh the negatives.

DR. CLANCY: Robert Clancy. I voted yes also for the same reasons already discussed.

DR. FOUNTAIN: Nathan Fountain. I voted yes. I'd also add that the more traditional biomarker of measuring the effect of the protein on the tetramers was convincing to me, although we didn't discuss that much or its methodology.

DR. KATZ: Can I go first? I'm sorry. Those folks who voted yes and have said for the same reasons, could you just be explicit as to which of the endpoints you are considering the surrogate, for purposes --

DR. FOUNTAIN: If I could summarize, I think it's the small fiber neuropathy, particularly part of the sigma 3, muscle strength testing, as part of the NIS-LL. And I added even the convincing but admittedly unknown methodology of actually testing the tetramer in binding and kinetics, the blood test.

DR. KATZ: Right. I understand that, though, as an aggregate of what the people are voting yes for, but it would be useful for us to know just specifically what each person considered in their yes vote.

DR. FOUNTAIN: Should we begin again with Dr. Ensrud?

DR. KATZ: Some people said it. I think Dr. Clancy.

DR. ENSRUD: As I mentioned, TTR stabilization and then the sigma 3 small fiber sum score.

DR. ROSENBERG: Same for me.

DR. GOOCH: Small fiber subscore and strength. Although I am intrigued by the physiologic data from the TTR assay, I'm not sure that there's a direct clinical link there in terms of its clinical effects. It makes sense, of course, but these other measures, small fiber function and strength, are clearly validated as having direct clinical impacts on a patient's function.

DR. LOGIGIAN: Muscle strength.

DR. MIELKE: All three.

DR. CLANCY: Yes. The muscle strength, the sigma 3 scores, and the very sexy TTR assay, whatever it means.

DR. FRANK: Samuel Frank. I voted yes. And what was most convincing to me was the TTR stabilization. And getting back to this being a lifelong disease, it also raises the question of whether genetic testing should be done in kids and whether that should start as early as possible, based on that stabilization, too, if that's truly the mechanism of the disease.

MS. HOUSE: Tiffany House. I voted yes for the TTR analysis and for the muscle weakness.

DR. MARDER: Ellen Marder. I voted yes for two reasons. One is the muscle strength and the other is the small fiber measurement, which seemed to keep -- let's see, the treated versus the controls seemed to preserve a distance even when the controls started to take the medication. They still seemed to do better in the 006 study as time goes on.

DR. BAGIELLA: Emilia Bagiella. I voted no because, although there is an effect, a possible effect

of the drug on this marker, it was not clear to me that this marker are really surrogate endpoints for the clinical outcome. There was no evidence of that.

DR. OAKLANDER: Anne Louise Oaklander. I voted yes on the basis primarily of the outstanding results for the tetramer stabilization. I would comment also that the measures used to evaluate small fiber function are not the ones identified as optimal by the American Academy of Neurology and the European Federation of Neurological Societies.

So I would suggest consideration in future studies of the addition of skin biopsy and of other small fiber measures in AFT. The sweat test, actually, has been shown to be more sensitive in many cases. So I'd like to see these small fiber measures expanded in future study.

DR. VERMA: Ashok Verma. I voted yes. Number one, good basic science, molecular basis with the TTR analysis, and motor strength.

DR. PRESTON: David Preston. I voted yes. In regards to the muscle strength and the small fiber testing, I was actually not impressed at all by it, and

I think it has the problems of multiple testing. But the TTR stabilization was so robust and the fact is that it makes sense.

So I actually do believe that this is the mechanism of the amyloid deposition. So this drug was so convincing as far as stabilizing that tetramer so it wouldn't break down, it makes so much sense, it fits together, that I think maybe a longer trial will show clinical efficacy.

DR. CHAUDHRY: I'm Vinay Chaudhry. I voted no. I wasn't convinced with the muscle strength or the small fiber data. And for the reasons that were mentioned, the 006 study did not pan out with small fiber. And I was more convinced with that being noise and the muscle strength testing suffered from the multiple testing issue. It did not form a length-dependent pattern of muscle weakness.

TTR is clearly robust, but I still am not convinced that that leads to a clinical benefit, since the quality of life did not change in any of these. So I'm not sure how to relate this to the clinical benefit. Therefore, I voted no.

DR. SHEFNER: I'm Jeremy Shefner. I voted no. I think all of the clinical endpoints, either in aggregate or broken down, are not particularly robust, didn't reproduce when the study was looked at without that single site.

I am completely convinced that there's an effect on the TTR stabilization, but I don't think there is a strong argument to be made at this point that, that has a particular implication on the clinical disease. And I also want to note that some of our microphones are still flashing and some of them aren't. I don't know if that's a problem.

DR. COHEN: Jeffrey Cohen, a tortured no. I think, again, because of the way this study was constructed, that those data from the Portugal study were so different from the others. Also, just clinically, some of the results being positive in some measures and others being negative, as we said, about sensory testing, some of the small fiber function, just doesn't make sense clinically to me.

DR. FOUNTAIN: Thank you. Next is question 3.

Given our response to questions 2A and 2B, do you still want us to answer question 3? Dr. Katz?

DR. KATZ: We're discussing it. I think our intention was, if you didn't think there was substantial evidence for anything, clinical, or biomarker, or surrogate, do you think Study 005 could be one study contributing --

DR. SHEFNER: I'd like to vote on it.

DR. FOUNTAIN: So we're resolving whether or not we're going to change the wording of question 3, since as written, it's --

DR. KATZ: I don't think it's necessary to vote on that question.

DR. FOUNTAIN: Okay.

So that means we'll move over to question 4 on the back side and projected on the screen, regarding Study 006. Study 006 does not have the characteristics of an adequate and well-controlled trial, but may provide supportive evidence of effectiveness for tafamidis.

Please discuss the strengths and weaknesses of Study 006 as a source of supportive evidence,

including the effect of the following factors. And some of these, we have discussed, but why don't we go down the line and see if there is issues we need to discuss further? And then we may need to clarify some issues even if we don't agree on them.

First is analysis of many endpoints without control for multiple testing.

DR. KATZ: Again, you have voted as a committee that there is substantial evidence of effectiveness for an effect on a surrogate. I think that your views specifically with regard to the regulatory implications of Study 006 are less important at this point.

DR. FOUNTAIN: Would you like us just to move to question 5 and vote or skip it?

DR. KATZ: We can go to 5. It's also sort of moot. Right. I think it's not necessary to vote on 5. It would be nice to have a little discussion about 6, I mean, if there's anything else that maybe you want to throw some comments in about, 006 or something.

DR. FOUNTAIN: It seems to me there's a topic we haven't discussed that's come up now as kind of a

recurrent theme, and that is the TTR testing that we haven't talked about so much.

If you have another comment, Dr. Logigian?

DR. LOGIGIAN: With regard to that, I don't know if Dr. Kelly is still here. But with regard to the TTR testing, I was wondering, is there a way to measure in serum the toxic monomer? That you could then use -- first of all, that's closer to the stabilization issue, is closer to the toxic compound.

DR. FOUNTAIN: Dr. Kelly?

DR. KELLY: That's an excellent question. I know at least two independent organizations that are trying to develop antibodies to do that, and my lab is trying to use a subunit exchange experiment. So we're working on that, but it's not available today that I'm aware of.

DR. LOGIGIAN: Can I ask a follow-up question?

DR. FOUNTAIN: Yes.

DR. LOGIGIAN: Is it true that this is actually a heterogeneous compound in someone with FAP? That is that they would have a mixture of wild type and

mutant monomers, and that there could be five different potential -- I don't know -- five or six combinations, three of one, one of another, two and two, et cetera? And do you think the drug has equal effect on all of those different compounds, that is, in terms of stabilizing them or are some potentially less bound?

DR. KELLY: It's an excellent question. I think each different mutation and each heterotetramer will have a slightly different binding constant. Now, that said, the KD at the first site is 2 nanomolar and the plasma concentration is 4 micromolar. So the issue came up earlier about albumin binding, too. I mean, basically, 99 percent of the tafamidis in plasma is going to be bound to transthyretin unless the sites are saturated. Then we'll go to albumin for sure. So your question is a really good one and that's the answer.

DR. FOUNTAIN: Dr. Katz?

DR. KATZ: Yes. I have a question. Again, part of the issue for us is where in the chain of events this surrogate falls. So for TTR, it's obviously very, very early in the chain, presumably perhaps the inciting event. But the end of the chain

is the deposition of amyloid, which presumably is what's doing the damage to the tissues.

So is there any in vivo data that looks at amyloid deposition in a model or in people? I gather there are no biopsies in people on treatment versus no treatment?

DR. KELLY: As you probably know, Dr. Katz, there have been two recently approved amyloid imaging agents, both based on PET. To my knowledge, they've never been attempted for transthyretin amyloidosis.

In the early days of FoldRX, we purposefully avoided that for the following reason, that patients who respond to light chain amyloidosis therapy and our observations in this study as well with regard to cardiac function, suggest that the wall thickness of the heart doesn't change even in the responders, suggesting that the amyloid doesn't change.

Now, I know there are many reports to the contrary. But if you actually read those papers, the title is opposite to the data. That is, there's very weak evidence for amyloid clearance over five years.

So I personally think it would be a mistake

to look at amyloid load because the emerging theme in the literature is that probably what our body does to protect us from these terrible diseases is to make amyloid, ironically. It's sort of like building a moat around the cell to keep all the crap on the outside, but that's still a hypothesis.

DR. FOUNTAIN: While you're up there, can I ask you to clarify one other thing? And that is, you might imply from the results, as they're listed, that the drug works 100 percent or zero, but the percent is actually a change in the rate constant or something like that. Could you clarify the percent change that is listed as the outcome from the study?

DR. KELLY: Without trying to make this too complicated, I'm happy to work with you folks afterwards.

Can we call up slide CP5?

DR. FOUNTAIN: The nature of my question, just to clarify, not so much the basic chemistry, just so we can put in perspective, if something can change 200 percent or 300 percent, then 100 percent has less meaning.

DR. KELLY: So the bottom line is that, under physiologic conditions -- so this is a subunit exchange experiment. So Dr. Farkas and Dr. Katz didn't see this. This is actually accepted for publication in P&S, and it's been reviewed by Science and other published articles.

What we do here is to take two tetramers. One has a tag and one doesn't. And the idea is, how fast can they exchange subunits, reflecting the rate of dissociation?

As you can see, the rate of dissociation at Cmin and Cmax is incredibly slow for the wild type tetramer at drug concentration. So what Dr. Farkas brought up in the briefing document is correct, that is, that there's roughly a two- to threefold slowing in the presence of drug. But you have to realize that's in a 4.8-molar urea, where the binding constant takes a huge hit and the rate of dissociation is dramatically accelerated. So the only reason we use that assay is we can measure it in a couple of days.

You can see here we're already out to eight days and we only have 5 percent exchange. Right? So

this protein is really kinetically stable. I hope that answers your question. So it's virtually 100 percent under physiologic conditions. That's what makes it so hard to measure.

DR. FOUNTAIN: Dr. Rosenberg? Dr. Clancy?

DR. CLANCY: He just answered it.

DR. FOUNTAIN: So we're on the theme of additional aspects of efficacy that might be measured. And the one we just talked about was TTR. Any other questions about it or clarifying issues? Dr. Frank?

DR. FRANK: This is in regard to question 6. Yes?

DR. FOUNTAIN: Yes.

DR. FRANK: So something that Dr. Coelho said in passing -- and I hope I heard her correctly -- is that 41 of the 44 patients removed themselves from the liver transplant list when they were on this longer term. Is that correct?

So I also want to raise the question of the efficacy of liver transplant. I mean, we assume that it works, but what's really the evidence? And right now, that's the gold standard. There are many surgical

procedures that we assume work. And then when we do more controlled studies, it turns out they don't.

So I think that we have more for this drug than we do for liver transplant, especially if there's longer- term evidence that could follow up on it.

DR. FOUNTAIN: Any more discussion about question 6? Question 7 is, "Please discuss if there are any particular concerns about safety," which we approached to some degree before. And our conclusion was, it's a small end, but there are no particular concerns.

DR. GOOCH: I have a question about the bladder issues. And I know that a neurogenic bladder can be a part of this disease process. And I wonder if the sponsors could comment on that particular adverse event that came up in the safety data.

DR. FOUNTAIN: What comment would you like them to make? Is that mechanistically, or if it's coincidence, or other?

DR. GOOCH: Just comment on that particular side effect in the treatment group versus placebo group. It did kind of show up among the top four

adverse events in the study. Does the data support that primarily as an issue related to the underlying disease process alone, which we know it can be? Was there any indication that the drug itself might exacerbate a neurogenic bladder in a patient with this condition?

DR. LOMBARDO: So I think, if I understand you correctly, you're speaking about the UTIs that were recorded?

DR. GOOCH: Yes.

DR. LOMBARDO: I'm actually going to ask Dr. Susan Mather from our safety group to come up and speak to that specifically.

DR. MATHER: Hi. I'm Dr. Susan Mather from worldwide safety at Pfizer. And yes.

Let me see if we can pull up -- we might want to pull up -- yes, slide 26. So this is just a brief summary of some features of the patients who had urinary tract infections, which as you rightly pointed out, wouldn't be unexpected in this patient population.

Before I get into it, I might have to call my colleague, John Davis, up to talk a little bit about

mechanism, but I will say that the number of serious UTIs we saw was very, very small, even in this small population of patients studied. There were two. And by and large, the UTIs were treatable, didn't result in patients discontinuing from the study, and may have had something to do with the fact that some patients, because of their urinary retention, were self-catheterizing themselves.

So by and large, the adverse event itself is an unexpected, but that imbalance in the groups was something that definitely made us make note of this as an adverse drug reaction in the proposed labeling.

Does that get at your question?

DR. GOOCH: That's a good summary of the data. Any ideas, mechanistically, as to why -- or is there any hint that this might in some way functionally cause poor bladder emptying, or some kind of problem with the immune protection of the bladder, or anything of that nature?

DR. MATHER: I will say that, looking at the white blood cells, and absolute neutrophil, absolute lymphocyte counts, we were glad to see no evidence of

immunosuppression. As far as the other factors that you mentioned, I don't think there's any evidence that would explain it.

DR. FOUNTAIN: Dr. Clancy?

DR. CLANCY: Yes. Regarding the UTIs, do we know, were all the patients self-cathing or were they more likely to be in this infection group?

DR. MATHER: No. Not all of the patients were self-cathing. About a third of the patients on tafamidis -- no. Less than a third of the patients on tafamidis were and a few on placebo were self-cathing, who had UTIs. But no. Not all of the patients were.

DR. CLANCY: But if it's a third in the treated group and only a handful in the placebo, that might be the mechanism, that you're more likely to get an infection if you self-cath.

DR. MATHER: Yes. Definitely. That would definitely introduce the mechanism, but it wasn't quite a third. So in the UTIs we saw, only a small number of patients on tafamidis and a small number of patients on placebo were self-cathing. So sorry if I confused.

DR. FOUNTAIN: Are there more comments about

that? So if we summarize, then, question 7, discuss the particular safety concerns.

Dr. Chaudhry, do you have something to say before I summarize?

DR. CHAUDHRY: Yes. I mean, I generally don't bring this up as an adverse event, but I do think about it as an adverse event. Is there a cost estimated? Is there a yearly cost of this drug, say, in Europe, which is being used or is it not fair game to talk about it on this panel?

DR. KATZ: The cost? The question was, is it fair game to talk about the cost? Not here. That is not a consideration from the point of view of making a decision about approving.

DR. FOUNTAIN: I think we'd summarize question 7 by saying there are no particular safety concerns.

Anymore comments from the panel? Or would Dr. Katz like to make any summary comments?

DR. KATZ: I'd just like to thank everybody. It's obviously been a very difficult set of data and decisions, so it's really been extraordinarily helpful.

And again, thanks to the folks who spoke in the public session. This was very helpful, and we appreciate it.

DR. FOUNTAIN: Thank you. And I think this really illustrates the difficult job you have because all of us here on the panel, of course, especially after hearing such compelling stories, want to do all we can to help people with an inexorably fatal condition, but yet want to do what's right to find drugs that are effective and safe. So that's your mission that I think we can appreciate.

Thank you, everyone, for coming. Please remember to drop off your name badge at the registration table on your way out so they may be recycled. The meeting is adjourned. Thank you.

(Whereupon, at 4:33 p.m., the meeting was adjourned.)

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Janet Evans-Watkins

Audio Reporter

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